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The link between event-related potentials and cognitive dysfunction in Multiple Sclerosis: A systematic review

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Dedicatória

"I was taught that the way of progress is neither swift nor easy." Marie Curie

A todos as pessoas com Esclerose Múltipla.

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Resumo Alargado

Introdução

A Esclerose Múltipla (EM) é uma das principais causas de disfunção do Sistema Nervoso Central em jovens adultos. Ocorre mais frequentemente em mulheres, entre os 20-40 anos. Fatores imunológicos, genéticos e ambientais têm um papel importante na sua etiologia. A fisiopatologia da EM baseia-se na inflamação crónica, na desmielinização e na perda de neurónios. A última característica é a principal causa de dano neurológico irreversível.

Os critérios mais atuais para o diagnóstico de EM são os de McDonald revistos em 2017. Ao longo do tempo têm existido diversos critérios – Schumacher (1965), Poser (1983) e versões anteriores dos critérios de McDonald (2001, 2005 e 2010). Os critérios utilizados na atualidade podem ser aplicados tanto na prática clínica como na investigação e não têm como propósito invalidar diagnósticos prévios com critérios anteriormente aceites.

A EM é uma doença crónica e progressiva, podendo manifestar-se nos vários sistemas – motor, urogenital, sensitivo, sensorial e cognitivo. Os principais défices associados à disfunção cognitiva relacionam-se com a atenção, velocidade de processamento, memória e função executiva, evoluindo de forma diferente de doente para doente. Esta manifestação clínica tem um impacto negativo significativo na qualidade de vida dos doentes com EM, requisitando uma adaptação dos cuidadores, dos familiares e da dinâmica laboral e social. Apesar disto, a avaliação da disfunção cognitiva não é realizada por rotina, sendo que algumas barreiras que o pudessem motivar foram identificadas: falta de conhecimento acerca da disfunção cognitiva na EM, estigma associado a esta manifestação clínica, falta de treino dos profissionais de saúde para avaliar este défice neurológico e ainda a falta de recursos financeiros. São necessárias ações para que estas barreiras sejam erradicadas.

Existem vários conjuntos de escalas validados para rastrear e avaliação a disfunção cognitiva na EM – *Brief Repeatable Neuropsychological Battery* (BRN-B), *Minimal Assessment of Cognitive Function in Multiple Sclerosis* (MACFIMS) e *Brief International Cognitive Assessment for Multiple Sclerosis* (BICAMS). Relativamente ao tempo de aplicação dos conjuntos referidos, a MACFIMS é a mais demorada (aproximadamente 90 minutos), seguida da BRN-B (aproximadamente 50 minutos) e, por fim, a BICAMS (aproximadamente 20 minutos). Uma vez que a duração recomendada para uma consulta

de Subespecialidade em Neurologia (onde se insere a EM) é de 45 minutos para uma primeira consulta e 30 minutos para as seguintes (segundo o Regulamento n.º 724/2019 da Ordem dos Médicos), a aplicação destes conjuntos de escalas cognitivas não é sistemática em todos os doentes.

A função cognitiva também pode ser avaliada por entidades neurofisiológicas conhecidas como potenciais evocados de longa latência (PELL), sendo o P300, o N400 ou o *Mismatch Negativity* (MMN) os mais relevantes na prática clínica. Segundo Dinteren et al (2014), a amplitude do P300 poderá ser relacionada quantitativamente com processos cognitivos a decorrer enquanto que a sua latência estará correlacionada com o processamento da informação em si. Segundo Romero et al (2015), o N400 é associado à linguagem, com os seus componentes neuronais, com características léxicas e contextuais. Por fim, segundo Cheng et al (2013), o MMN relaciona-se com a memória sensorial auditiva. Todos os PELL referidos poderão ser usados no sentido de avaliar a disfunção cognitiva na EM.

Objetivo

Esta revisão sistemática da literatura (RSL) tem como objetivo responder à questão: podem os potenciais evocados de longa-latência ser uma ferramenta diagnóstica relevante da disfunção cognitiva na EM?

A deteção precoce da disfunção cognitiva na EM poderá possibilitar não só o doente, mas também os profissionais de saúde a intervir, por forma a retardar a progressão desta manifestação clínica, recorrendo a opções farmacológicas e não-farmacológicas. A importância desta RSL baseia-se em melhorar a qualidade de vida dos doentes com EM.

Métodos

Foram incluídos na nossa RSL estudos que abrangeram pessoas com idade igual ou superior a 18 anos, diagnosticadas com EM através dos Critérios de McDonald (de qualquer ano) e/ou de Poser e/ou de Schumacher, com ou sem queixas cognitivas e independentemente da duração da doença e da medicação habitual. Incluímos apenas três PELL – P300, N400 e MMN. Os comparadores escolhidos foram valores normativos dos PELL respetivos, escalas de avaliação cognitiva – nomeadamente *Mini-Mental State Examination* (MMSE), *Montreal Cognitive Assessment* (MoCA) e *Addenbrooke's Cognitive Examination* (ACE) – e grupos de controlo saudáveis. Os *outcomes* pretendidos foram a amplitude e/ou a latência dos PELL mencionados. Os estudos selecionados estariam escritos em Português, Espanhol, Inglês ou Francês. Seriam excluídos artigos de

revistas não submetidos a revisão por pares, publicações em congressos, revisões da literatura e estudos de caso.

Foram utilizadas quatro bases de dados – PubMed, Embase, Scielo e Web of Science, com a data-limite de 10 de março de 2021. A pesquisa foi realizada tendo em conta as especificidades de cada base de dados, utilizando uma combinação de palavras-chave, termos MESH ou EMTREE. Outros artigos relevantes que poderiam não aparecer na pesquisa inicial e que preenchessem os critérios de elegibilidade serão acrescentados aos resultados para uma eventual avaliação integral.

Inicialmente, foram eliminados os artigos repetidos e, posteriormente, foi realizada a avaliação de acordo com os títulos e *abstracts*, por dois autores de forma independente. Finalmente, foi efetuada uma leitura integral dos estudos selecionados e aplicados os critérios de elegibilidade.

O Risco de Viés foi avaliado através de *Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) Tool*, da Cochrane. A Qualidade dos Artigos foi estimada de acordo com *JBI Critical Appraisal Tools*.

Esta RSL apresenta-se como um estudo qualitativo, analisando os estudos de acordo com o *outcome* principal, ou seja, a variação da amplitude e/ou latência do P300, N400 ou MMN. Os dados foram considerados relevantes para a nossa RSL quando a comparação entre valores normativos dos PELL, escalas cognitivas ou grupos de controlo saudáveis e doentes com EM foi estatisticamente significativa, isto é, com $p<0,05$.

Resultados

Esta RSL teve por base 425 artigos, sendo que 424 foram obtidos através da pesquisa nas bases de dados referidas e um artigo foi acrescentado tendo em conta a sua relevância para a questão que pretendemos responder na RSL.

Os artigos duplicados foram eliminados (148), obtendo um novo total de 277 estudos. Destes, 206 foram excluídos através da avaliação de títulos e *abstracts,* selecionando, assim, 71 estudos para uma leitura integral. Desta avaliação final resultaram 26 artigos que foram incluídos para uma avaliação qualitativa.

Nesta RSL foram incluídos 1028 doentes com EM, com a idade média máxima de 50,90 ± 9,09 anos (em Whelan et al (2010)) e mínima de 28,88 ± 9,04 anos (em González-Rosa et al (2011)). Dezanove estudos referiram a duração da doença, variando de 15,2 ± 9,4 meses

(em Piras et al (2003)) até 13,8 ± 6,8 anos (em López-Góngora et al (2015)). *Expanded Disability Status Scale* (EDSS) foi avaliada em vinte e quatro artigos, cuja pontuação variou de 0,87 ± 0,91 (em López-Góngora et al (2015)) até 4,92 ± 2,2 (em Honig et al (1992)). Os critérios de diagnósticos mais frequentemente verificados nesta RSL foram os de Poser – em 462 doentes – e os de McDonald revistos em 2010 – em 300 doentes. Vinte e um artigos indicaram o padrão de EM que os doentes apresentaram, sendo a EM surto-remissão (presente em 695 doentes) o padrão de evolução natural mais referido. Apenas oito mencionaram a medicação habitual dos doentes, sendo que 256 estariam sob tratamentos imunomodeladores e 48 sob tratamentos com outros fármacos direcionados para outras doenças.

Vinte artigos recorreram a escalas cognitivas, contudo, apenas dois estudos compararam os PELL com o MMSE e três com o MoCA. Nos estudos que avaliaram o MMSE, apenas Honig et al (1992) demonstraram resultados estatisticamente significativos, comparando as pontuações obtidas pelo grupo de controlo saudável e pelos doentes com EM (menor pontuação). Em Zeng et al (2017) também se verificou a tendência de obtenção de menor pontuação no grupo de doentes com EM, mas a comparação com o grupo de controlo saudável não é estatisticamente relevante. Nenhum artigo avaliou o ACE. As principais escalas cognitivas incluídas nos artigos mencionados foram *Beck's Depression Inventory* (BDI), *Paced Auditory Serial Addition Test* (PASAT) e *Symbol Digits Modalities Test* (SDMT), em 7, 7 e 5 artigos, respetivamente.

Nos estudos que avaliaram o MoCA, as comparações das pontuações obtidas entre o grupo de controlo saudável e os doentes com EM foram estatisticamente relevantes em dois artigos (El-din et al (2016) e Zeng et al (2017)), sendo estas menores do grupo de doentes. Em Gedizlioglu et al (2021), apenas a comparação dentro do grupo de doentes com EM – em período de surtos ou em período de remissão – se demonstrou relevante, sendo a sua pontuação menor durante o primeiro período referido.

O P300 foi o PELL mais abordado – estando presente em vinte e cinco artigos –, demonstrando uma amplitude reduzida ou uma latência aumentada em 84% dos estudos (vinte um em vinte e cinco). Destes vinte e um estudos, em 57% (isto é, em doze) verificou-se a variação mencionada dos parâmetros do P300 simultaneamente. Em dezoito estudos foi obtido através da modalidade auditiva, em onze através da visual e os restantes quatro avaliaram as duas simultaneamente.

P300 auditivo:

Foi avaliado em dezoito artigos, sendo que, em treze desses estudos foi obtido através do paradigma *oddball*. A sua amplitude demonstrou-se reduzida em nove estudos, não teve resultados estatisticamente significativos em sete e não foi mencionada em dois. A latência deste PELL verificou-se aumentada em quinze estudos, não teve resultados estatisticamente significativos em dois e diminuiu em um.

Destes dezoito artigos que avaliaram o P300 auditivo, oito não demonstraram variação de pelo menos um parâmetro do PELL (amplitude ou latência) e em nove verificou-se uma redução da amplitude e um aumento da latência simultaneamente.

P300 visual:

Foi obtido em onze estudos, recorrendo ao paradigma *oddball* em seis desses. A sua amplitude demonstrou-se reduzida em sete artigos, não teve resultados estatisticamente significativos em dois, aumentou em um e não foi avaliado noutro. A sua latência verificou-se aumentada em seis estudos, não teve resultados estatisticamente relevantes em quatro e não foi mencionada em um.

Dos onze artigos que avaliaram este PELL na modalidade visual, cinco não demonstraram variação de pelo menos um parâmetro (amplitude ou latência) e em quatro verificou-se uma amplitude reduzida e uma latência aumentada simultaneamente.

N400:

Foi avaliado em apenas um artigo, através da modalidade visual. Neste estudo verificou-se a redução da amplitude e o aumento da latência.

MMN:

Foi referido em dois estudos, através da modalidade auditiva. Num dos artigos, a sua amplitude não foi abordada e a latência diminuiu. No artigo restante, não foram obtidos dados estatisticamente relevantes.

Discussão

P300 auditivo:

A redução da amplitude e o aumento da latência simultaneamente demonstrou-se em nove dos dezoito artigos, isto é, em 50%. Separadamente, a latência verificou-se prolongada em quinze dos artigos referidos, ou seja, em 83,3%.

Apenas um estudo demonstrou a redução da latência deste PELL. Esta diferença poderá relacionar-se com a separação da onda P300 em P3a e P3b e com o facto do P300 auditivo ter sido obtido através do paradigma *passive oddball*, mais relacionado com P3a, não sendo possível valorizar este resultado à luz dos restantes.

Gedizlioglu et al (2021) concluíram que este PELL poderá ser um marcador de disfunção cognitiva durante os surtos, tendo em conta a sua praticabilidade e reprodutibilidade. Pokryszko-Dragan et al (2009) defenderam que os PELL seriam apenas uma ferramenta adjuvante na avaliação cognitiva dos doentes com EM, sendo os testes neuropsicológicos os principais métodos diagnósticos. Contudo, em 2016, concluíram que o P300 seria um método mais adequado para avaliação da disfunção cognitiva, tendo em conta que seriam mais objetivos e dariam uma avaliação global, contrariamente às escalas cognitivas. Waliszewska-Prosól et al (2018) sugeriram que o P300 auditivo seria um índice de disfunção cognitiva subtil, uma vez que todos os doentes obtiveram resultados normais através de testes neuropsicológicos, demonstrando que os doentes não apresentariam défices cognitivos detetáveis pelas escalas cognitivas. Por fim, Zeng et al (2017) reforçaram a importância deste PELL tanto na investigação como ferramenta complementar na prática clínica, relacionando-o com o MoCA na EM.

P300 visual:

Em onze artigos, quatro demonstraram uma amplitude reduzida e uma latência aumentada deste PELL simultaneamente, isto é, em 36,4%. Separadamente, a amplitude verificou-se diminuída em 63,6% dos estudos e a latência prolongada em 54,4%.

Um estudo relevou uma variação diferente – o aumento da amplitude. Neste artigo, o P300 visual foi obtido através de imagens de Kanizsa, ou seja, não foi usado o paradigma mais frequente.

Artemiadis et al (2018) confirmaram a relação entre a BICAMS e o P300, inferindo a importância deste PELL como indicador da função cognitiva. Magnié et al (2007) sugeriram que as variações dos parâmetros deste PELL antecediam as demonstradas pelo P300 auditivo e que ambas se verificavam previamente às alterações nas escalas cognitivas. Para além disto, em Magnié et al (2007) é reforçada a importância de incluir este PELL no diagnóstico e no follow-up da disfunção cognitiva na EM, antes que esta seja demonstrada pelos testes neuropsicológicos. Finalmente, Piras et al (2003) demonstraram a relevância deste PELL numa perspetiva diferente – quando a incapacidade física impossibilita a avaliação da função cognitiva através de escalas cognitivas.

N400:

Este PELL foi avaliado por Amato et al (2016), revelando uma redução da amplitude e um aumento da latência, através de um paradigma específico – *Stroop-Task* – que Liotti et al (2000) considera consequência da atividade do córtex cingulado anterior. Milosevic et al (2012) sugeriu que o N400 poderá ser um método indicativo da memória semântica na EM.

Uma vez que apenas um artigo mencionou este PELL, não é razoável assumir a sua aplicabilidade como método diagnóstico da disfunção cognitiva na EM.

MMN:

Jung et al (2006) não avaliaram a amplitude *per si*, mas sim, a sua área, argumentando que esta seria uma abordagem mais reproduzível. Este parâmetro demonstrou-se reduzido, tal como a sua latência. Jung et al (2006) sugeriram que estas variações – tal como as verificadas no P300 também avaliado neste estudo – poderão ser indicativas de um défice cognitivo subtil durante o período pré-clínico. Em Santos et al (2006) não se verificaram alterações estatisticamente significativas destes parâmetros. Neste estudo, os autores verificaram que este PELL estaria ausente em 40% dos doentes com EM durante o protocolo de variação da duração e em 45% no de variação da frequência. Santos et al avaliaram os doentes com o PASAT e concluíram que a disfunção cognitiva evidenciada por este teste neuropsicológico estaria relacionada com a ausência do MMN.

Tendo em conta que este foi o PELL com resultados mais discrepantes na RSL e que apenas foi abordado em dois estudos, não é possível inferir a sua importância diagnóstica na disfunção cognitiva nesta doença específica.

A nossa RSL poderá apresentar algumas limitações, nomeadamente, a menor amostra de doentes incluídos, considerando a prevalência mundial da EM, e os escassos dados de MMSE, MoCA e ADE obtidos dos estudos incluídos.

Conclusão

Os resultados obtidos nesta RSL sugerem que o P300 poderá ser um método diagnóstico apropriado para a disfunção cognitiva na EM, revelando esta manifestação clínica subtil previamente à sua deteção através de escalas cognitivas. Apesar do MMSE, do MoCA e do ACE serem os testes neuropsicológicos mais utilizados na prática clínica, poderão não ser

os mais indicados para a avaliação precoce desta manifestação clínica. Os PELL poderão fornecer dados acerca da função cognitiva previamente às escalas cognitivas, o que, aplicado sistematicamente, poderá ter um impacto significativo na melhoria da qualidade de vida dos doentes com EM.

Mais estudos comparando os doentes com EM com as escalas cognitivas mais usuais na prática clínica – MMSE, MoCA e ACE – e os PELL mencionados são necessários para implementar estas entidades neurofisiológicas de forma permanente na abordagem clínica à disfunção cognitiva na EM, e não apenas como ferramenta alternativa.

Palavras-chave

Esclerose Múltipla;Potenciais Evocados de Longa Latência;Disfunção Cognitiva.

Abstract

Introduction: Multiple Sclerosis is one of the most frequent causes of Central Nervous System disease in young persons. It is associated with cognitive impairment in 70% of cases, resulting in a diminished quality of life. This systematic review aimed to evaluate if event-related potentials (ERPs) can be a relevant diagnosis tool of cognitive dysfunction in MS.

Methods: Four databases were consulted (PubMed, Embase, Scielo and Web of Science) until March 10th, 2021. The research was made combining keywords, MESH or EMTREE terms. The inclusion criteria were 1) ≥ 18 years old, 2) diagnosis according to specific MS criteria, 3) with or without cognitive complaints, 4) independently of the time of diagnosis and usual medication, and 5) articles written in Portuguese, Spanish, English and French. Papers should use ERPs, compared with normative values, Scales of Cognitive Evaluation and/or healthy control groups. The expected outcome was ERPs amplitude and/or latency variation (P300, N400 and mismatch negativity – MMN).

Results: 425 articles were obtained initially, with 26 articles in the end. P300 was the most discussed ERP (25 articles), demonstrating a reduced amplitude or an increased latency in 84% of those. N400 was evaluated in one and MMN was addressed in two articles. ERPs were compared with Mini-Mental State Exam in two of them and with Montreal Cognitive Assessment in three. Other scales were also compared with ERPs in twenty articles.

Conclusion: MS patients with cognitive impairment demonstrated overall ERP abnormalities, suggesting that ERPs may be an appropriate diagnostic method for cognitive impairment in MS.

Keywords

Multiple Sclerosis;Event-Related Potentials;Cognitive Dysfunction.

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List of Abbreviations

10/36 SR	10/36 Spatial Recall
AVLT	Rey Auditory Verbal Learning Test
BDI	Beck Depression Inventory
BIMCT	Blessed Information-Memory -Concentration Test
BNT	Boston Naming Test
BRBNT	Brief Repeatable Battery of Neuropsychological Tests
BRB-N	Brief Repeatable Battery
BVMT-R	Brief Visuospatial Memory Test – Revised
BVRT	Benton Visual Retention Test
CET	Concentration Endurance Test
CI	Cognitive Impairment
COWAT	Controlled Oral Word Association Test
CVLT	California Verbal Learning Test
DI	Deterioration Index
EDSS	Expanded Disability Status Scale
EHI	Edinburgh Handedness Inventory
ERPs	Event-Related Potentials
FSS	Fatigue Severity Score
GBT	Grober and Buschke Test
HADS	Hospital Anxiety and Depression Scale
HRS	Hamilton Rating Scale
KCFS	Kurtzke Cerebral Function Scale
MMN	Mismatch Negativity
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MS	Multiple Sclerosis
MSFC	Compound Functional Measure for Multiple Sclerosis
MSSS	Multiple Sclerosis Severity Score
MSQoL-54	Multiple Sclerosis Quality of Life-54 Instrument
NART	National Adult Reading Test
PASAT	Paced Auditory Serial Addition Test
PSS	Perceived Stress Scale
RPCM	Raven's Progressive Colored Matrices
SDMT	Symbol Digits Modalities Test
SRT	Selective Reminding Test
TMT	Trail Making Test
VSS	Visual Spatial Supraspan
VST	Visual Search Test
WAIS	Wechsler Adult Intelligence Scale
WCST	Wisconsin Card Sorting Test
WMS-R	Wechsler Memory Scale – Revised

1. Introduction

Multiple sclerosis (MS) is one of the most frequent causes of Central Nervous System (CNS) disease in young adults (1). It is more frequent in women and typically occurs in young adults (20-40 years) (2). The etiology of MS is multifactorial, in which immunological, genetic, and environmental factors play an important role (1). MS patients present cognitive impairment in up to 70% (3), although it is not systematically assessed in clinical practice (4). This clinical manifestation entails a reduction in patients' quality of life, requiring an adaptation of their life and of their social network (4).

1.1. Multiple Sclerosis

1.1.1. Physiopathology

MS presents several changes in CNS such as chronic inflammation, demyelination, plaque formation (gliosis), and neuronal and axonal loss (2). Inflammatory mononuclear cells – T cells and macrophages – lead to the formation of new MS lesions through perivenular cuffing, which culminates in the disruptions of the blood-brain barrier (BBB) at sites of lesion (2). In MS, the myelin sheath of the axon has myelin-specific autoantibodies, and its degeneration represents the hallmark of the disease – and one of the first changes to appear (2). Plaque formation may occur due to the remyelination of the surviving axons by oligodendrocytes (2). The last characteristic – neuronal and axonal loss – is the principal cause of irreversible neurological disability (2).

1.1.2. Diagnosis

Over time, there have been several criteria to diagnose MS. Some examples of those are Schumacher's (1965), Poser's (1983) and McDonald's (2001, 2005, 2010 and 2017) (5). These are specified in Appendix 1.

These Criteria should enable an earlier diagnosis based not only on clinical characteristics but also on imaging through MRI and on other biomarkers (such as, CSF analysis), potentiating suitable management of this clinical condition (6). The most recent version of McDonald Criteria (2017) can be applied in clinical practice and also in research, and it has no intention of invalidating previous MS diagnosis with other criteria (6). It is also crucial to correctly apply the most appropriate MS treatment, including disease-modifying therapies, that could be contraindicated in several differential diagnosis of this condition (6). 2017 McDonald Criteria revised suggest that additional studies including evoked potentials (visual, motor and somatosensory) should be addressed in order to possibly be included in MS diagnostic criteria (6).

1.1.3. Clinical Course of MS

MS may present a relapsing-remitting or a progressive course. In the first one, we observe relapses – clinical episode of signs and symptoms of MS that lasts at least 24h in the absence of fever or infection (6) – with neurological stability between episodes (7). In the second one, there is a constant neurological impairment with worsening. It can be primary when it becomes progressive after the first episode of MS or secondary when it acquires a progressive course after a relapsing-remitting period (7).

1.1.4. Clinical Manifestations

This chronic and progressive disease provokes signs and symptoms in several areas – motor, urogenital, sensitive, sensorial, coordination and cognition – due to the diffuse presence of plaques in the brain and spinal cord (1).

The main deficits associated with cognitive impairment are related to attention, processing speed, memory, and executive function, being present in up to 70% of patients with multiple sclerosis (3). It is noteworthy that cognitive dysfunction can evolve differently in each MS patient, being possibly related to MRI cerebral lesions but not to disease duration (8) or to Expanded Disability Status Scale (EDSS) (9).

MS patients tend to have a diminished quality of life, which results in the requirement for the help of caregivers and changes in the family, work and social dynamics (10). Cognitive impairment reveals its impact in several areas of daily-life, such as a higher probability of being unemployed, less ability and safety to drive, less informed decisions in medical decision-making, poor treatment adherence, and reduced money management capacity (4).

Despite all of this, assessment of cognitive dysfunction is not routinely performed (4). Some barriers are identified as the reason for this – the lack of knowledge about cognitive dysfunction seen in MS (in patients themselves, family members, or healthcare professionals), the stigma related to this type of impairment, the lack of appropriate training of clinicians to evaluate cognitive dysfunction, the insufficiency of financial resources – and it is necessary to take actions to eradicate these barriers (4).

One recommendation common to all patients with MS is the necessity to improve patient and professional education about cognitive dysfunction, its consequences, and its management (4).

1.2. Cognitive Scales

Since the basic neurological exam or the Mini-Mental State Exam (MMSE) are insufficient to access cognitive dysfunction specifically in MS (11), there are several validated screening and evaluation batteries of tools used in MS – Brief Repeatable Neuropsychological Battery (BRN-B) – including Paced Auditory Serial Addition Test (PASAT), Single Digit Modalities Test, Selective Reminding Test (SRT), 10/36 Spatial Recall Test (10/36 SRT) and Controlled Oral Work Association Test (COWAT) –, Minimal Assessment of Cognitive Function in MS (MACFIMS) – including PASAT, Single Digit Modalities Test, California Verbal Learning Test 2 (CVLT2), Brief Visuospatial Memory Test Revised (BVMTR), COWAT, Judgment of Line Orientation Test and Delis-Kaplan Executive Function System Sorting Test – and Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) – including The Symbol Digit Modalities Test (SDMT), CVLT2 and BVMTR (4,9,12). Besides these, several other cognitive scales are validated in this condition – Multiple Sclerosis Functional Composite (MSFC), Processing Speed Test (PST), Computerized Speed Cognitive Test (CSCT), Wechsler Memory Scale III (WMS-III), Continuous Performance Test (CPT), Wechsler Adult Intelligence Scale III (WAIS-III), Wisconsin Card Sorting (WCST), Stroop Test, Multiple Sclerosis Quality of Life-54 (MSQoL-54) and Modified Fatigue Impact Scale (4,9,12). It is possible that this variety of cognitive scales existent and the non-standardization of an assessment routine in this area may cause a decrease in its application in clinical practice.

Regarding the time needed for these batteries of cognitive scales, MACFIMS is the one that takes the longest – approximately 90 minutes –, followed by BRN-B (50 minutes) and by BICAMS (20 minutes) (9). Since the standard duration recommended for an appointment in a subspeciality in Neurology – such as Multiple Sclerosis – is 45 minutes for the first consult and 30 minutes for the following (13) and not forgetting the barriers to cognitive evaluation mentioned previously, it is frequently impossible applying these batteries of cognitive scales systematically in each MS patient.

The Consortium of Multiple Sclerosis Centers and International Multiple Sclerosis Cognition Society currently recommend a first assessment of cognitive function with SDMT or other validated scales when the patient is clinically stable (4). Its reevaluation with the same neuropsychological test should be made annually or as needed to evaluate treatment effects, cognitive impairment progression, or changes within disease activity (4).

1.3. Event-Related Potentials

A non-invasive quantitative method that can be used to evaluate brain functioning is electroencephalography (EEG). However, it may not specific enough to provide information about cognitive processing. Other neurophysiological entities are available named event-related potentials (ERPs) (14) – more precisely P300, which is the more studied event-related potential (ERP) (15). ERPs are normally acquired by an EEG/evoked potentials machine.

Evoked Potentials are characterized by a change in electrical potential directly associated in time with a certain stimulus or process (16). Its complete waveform present positive – P – and negative – N – deflections (16). The names attributed to the several ERP components are a consequence of their polarity (P or N) and approximate latency – P100, N100, P200, N200, and so on (17). P300, N400 and Mismatch Negativity (MMN) are the more relevant and useful evoked potentials in clinical practice (14).

Guideline number 021/2012 written by *Direção-Geral da Saúde* in Portugal – relatively to annual organization of MS patients care – do not refer that cognitive event-related potentials should be integrated on its management (18).

1.3.1. P300

P300 is a positive component observed at about 300 milliseconds and it is associated with the beginning of a task-relevant and rare stimulus (14). Thus, is highly dependent on patients' attention (14). One of the most used paradigms to obtain this ERP is the oddball paradigm, demonstrating how the brain differentiates stimuli and processes probability (14). There are different stimulus factors within the two main stimulus form – auditory and visual: frequency, duration, intensity, interstimulus interval, dimension of change and probability (14).

According to context-closure hypothesis – which tries to identify the important cognitive processes underlying P300 –, Dinteren et al (17) suggested that its amplitude may be correlated quantitatively with cognitive processes in progress and its latency may be more related to velocity of processing information itself. Besides this, patients with schizophrenia, Alzheimer's disease, and people at high risk for alcoholism are associated with a reduced P300 amplitude (14). It is also proved that age influences P300, both in latency and in amplitude (17). In older adults, P300 latency increases, and amplitude tends to be lower (17). A reduced amplitude tends to be associated with a worse performance on several cognitive tests, which may be indicative of different aspects of

information processing (17). Because of these characteristics, P300 may be a potential indicator of cognitive function in multiple clinical situations (14).

1.3.2. N400

N400 appears as a negative component 400 msec after the stimulus begins. The amplitude of this ERP is related to the conceptual knowledge associated with a word and the incapacity of rescuing that (14). N400 is associated with language, its neural components and lexical and contextual features (19). Several stimulus factors are associated with this ERP: congruity, semantic relationships, lexical factors, word frequency, concreteness, orthographic neighborhoods, probabilities, memory/learning, duration and interstimulus interval (14).

1.3.3. MMN

The mismatch negativity is observed when a certain stimulus discontinues the ongoing regularity, even when lack of attention is verified (14). Therefore it is relevant to evaluate young or dysfunctional patients and their auditory sensory memory and stimulus-change discrimination (20). MMN is characterized by a waveform with 0.5-5 μV negatively in amplitude and a latency period of 100-250 msec (14). A commonly used paradigm to obtain this ERP consists in present a sequence of repeated standard sounds quickly and interrupt those with a rare deviant sound occasionally (14). Contrary to the P300, no attention is required to obtain this response (14).

Aging is associated with a relevant deterioration of MMN both in duration and in frequency (20). MMN can also be used to quantify the cognitive decline in MS – it is associated with a more prominent reduction of this ERP in patients with cognitive impairment than in those without (14).

1.4. Objectives

This systematic review of literature (SRL) aims to try to answer the question: can event-related potentials be a more relevant diagnosis tool of cognitive dysfunction in MS?

Being able to answer positively to this question can be a crucial paradigm shift for MS patients who deal constantly with the personal and social load of this disease, including with the stigma associated with cognitive dysfunction. Detecting possible cognitive impairment earlier may capacitate not only the patient itself but also health professionals to take action to slow down the progression of this manifestation, with pharmacological

and non-pharmacological options. The relevance of this question – and consequently of our SRL – lies in improving substantially MS patients' quality of life.

2. Methods

2.1. Eligibility Criteria

According to PICO Framework, in our SRL were included studies that evaluated humans with 18 years old or more, with diagnosed MS according to McDonald criteria and/or McDonald criteria revised (any year) and/or Poser criteria and/or Schumacher criteria, even without cognitive complaints, independently of the time of diagnosis and of usual medication. We used the diagnostic test as the intervention and included the event-related potentials – P300, N400, mismatch negativity (MMN). Comparisons chosen were normative values of ERPs, Cognitive Evaluation Scales – specifically the Mini Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA) and Addenbrooke's Cognitive Examination (ACE) – and comparison with healthy control groups. The selected outcomes the amplitude and/or latency of event-related potentials (P300, N400, and mismatch negativity). Articles selected were written in Portuguese, Spanish, English, and French. Inclusion and exclusion criteria are summarized in Table 1.

Table 1 – Summary of Inclusion and Exclusion Criteria.

Inclusion Criteria	Exclusion Criteria
Humans > 18 years old. Diagnosed with MS, according to McDonald criteria and/or McDonald criteria revised (any year) and/or Poser criteria and/or Schumacher criteria. With or without cognitive complaints. Independent of time of diagnosis and usual medication. Diagnostic test: Event-related potentials – P300 and/or N400 and/or MMN. Comparisons with ERPs normative values or Cognitive Evaluation Scales – MMSE, MoCA and ACE – or healthy control groups. Outcomes: ERP amplitude and/or latency (P300; N400; MMN). Articles written in Portuguese or Spanish or English or French.	Articles full-text in other languages non explicit in Inclusion Criteria; Articles non-submitted to peer-review journals, conference proceedings, conference papers, author review articles, case studies, systematic reviews and metanalysis.

2.2. Search strategy

In this SRL four data bases were consulted – PubMed, Embase, Scielo and Web of Science – until March 10th, 2021. The research was made according to the criteria and specifications of each database, combining keywords, MESH or EMTREE terms. The terms used to the research are specified in Appendix 2.

Other relevant articles that were known to the researchers that might not appear in the initial search and that met the inclusion criteria would be added to the results for eventual full-text evaluation.

2.3. Data Collection and Analysis

2.3.1. Article Selection

Using the EndNote Software, a first selection of the initial articles was made, where the repeated ones were excluded. In this new total, a second selection was made by J. F. and A. V. P, separately. The inclusion and exclusion criteria were applied in the titles and abstracts of each article. In case of discrepancy, a third person – N. P. – was involved in the process. Not all articles and data were available and so the authors were contacted asking to provide them. Posteriorly to the analysis of full-text, authors were contacted through email to clarify some points of the respective article – such as peer-review, type of study, follow-up, process of selection of controls and/or patients (i.e., randomization), diagnostic criteria of MS patients, other ERPs studied and non-included (P300 or N400 or MMN) and use of other scales (MMSE or MoCA or ACE).

2.3.2. Data Extraction

Simultaneously, an Excel table was created to collect and synthesize the essential information. The topics included were: author, title, eligibility (first selection and full-text), database, type of article, language, year of publication, journal of publication, participants (total number), controls (total number, education, sex and average age), MS patients characteristics (total number, education, sex, average age, diagnostic criteria, duration of the disease, type of MS, number of relapses, usual medication, years of medication, symptoms of cognitive dysfunction, EDSS, and other conditions associated – depression, sleep disturbances, other psychiatric diseases), cognitive evaluation scales, MRI information (number/purpose and average lesion), lumbar puncture/CSF information (oligoclonal bands and other informations), EEG (type/system, situation, stimulation parameters, reaction time, P300 – amplitude and latency –, N400 –

amplitude and latency –, MMN – amplitude and latency –, other ERPs – amplitude and latency – and other potentials – VEP, SSPE, BAEP and AMLR), results/conclusions and limitations of the study.

2.4. Risk of Bias

The potential risk of bias was evaluated using *Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) Tool* by Cochrane (21), with the support of Review Manager (RevMan5).

2.5. Quality Assessment

Quality was addressed by JBI Critical Appraisal Tools (22), evaluating relevance and results of each article, where several questions should be answered: 1) Were the criteria for inclusion in the sample clearly defined?; 2) Were the study subjects and the setting described in detail?; 3) Was the exposure measured in a valid and reliable way?; 4) Were objective, standard criteria used for measurement of the condition?; 5) Were confounding factors identified?; 6) Were strategies to deal with confounding factors stated?; 7) Were the outcomes measured in a valid and reliable way? and 8) Was appropriate statistical used?.

2.6. Data Synthesis

When developing this SRL, we sought to carry out a qualitative study, analyzing the studies according to the main outcome, that is, the variation of amplitude and/or latency of P300 or N400 or MMN. Studies were aggrouped by the main ERP studied and, if applicable, by the modality (visual or auditory) used to obtain it. The relevant data to our SRL was considered significant when a statistically relevant difference – with $p<0,05$ – between ERPs normative values or Cognitive Evaluation Scales or healthy control groups and MS patients was verified.

To improve organization of the suitable data and to improve their discussion, outcomes were divided according to the variation of ERPs parameters: A) Only Reduced Amplitude, B) Only Increased Latency, C) Reduced Amplitude and Increased Latency Simultaneously and D) Others (i.e., without variation of both parameters or with results non consistent with groups above mentioned). In summary of each study the results of neuropsychological tests will also be mentioned if applicable.

3. Results

3.1. Article Selection

The search of the four databases above mentioned resulted in 424 articles (68 from PubMed, 207 from Embase, 149 from Web of Science and none from Scielo). Another article that did not appeared in the mentioned research, but met the main eligibility criteria, was posteriorly added because of its relevance to the question that we aim to answer in our SRL. Therefore 425 records were obtained initially and are the foundation of this work.

Using EndNote software, the duplicates were eliminated (148), resulting in 277 articles (187 from Embase, 9 from PubMed, 80 from Web of Science and 1 from other source).

After title and abstract analysis, 71 articles were selected to full-text reading and so 206 articles were excluded (4 from PubMed, 131 from Embase and 71 from Web of Science) – 92 studies due to the type of article, 19 studies didn't have subjects with cognitive dysfunction, 33 studies didn't apply ERPs, 3 studies due to full-text language, 3 studies wanted to study a specific drug effect, 48 studies didn't have MS patients, 5 studies were applied on pediatric population and 3 studies demonstrated an inappropriate intervention (based on computer interfaces).

After full-text reading and according to the respective answers of the authors, 26 articles were included and 45 were excluded – 6 due to unavailability of full-text, 16 due to study design, 7 due to inadequate intervention, 3 due to inadequate comparator, 9 due to inadequate outcome and 4 due to overlapping population (i.e., populations presented in these articles were similar to those described in other studies already considered).

PRISMA diagram is illustrated in Figure 1.

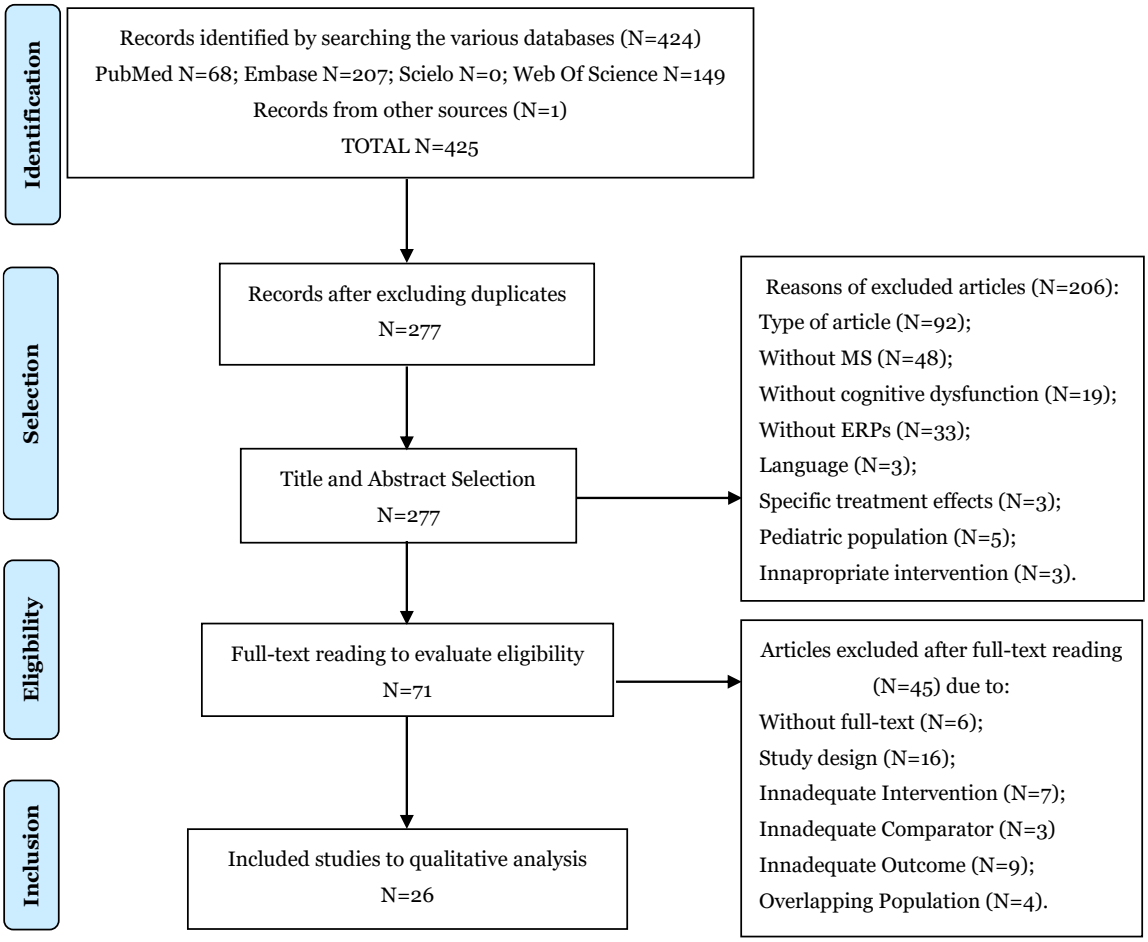

Figure 1 – PRISMA diagram representing the process of Article Selection (adapted from (23)).

3.2. Study Characteristics

In total, 1028 MS patients were included in this SRL – 390 males, 618 females and 30 undefined in the article (24). The article with the highest mean age was by Whelan et al (25), with 50,90 ± 9,09 years, and the article with the lowest mean age was by González-Rosa et al (26), with 28,88 ± 9,04 years.

Regarding the diagnostic criteria used, 31 MS patients were diagnosed with Schumacher Criteria (27), 462 with Poser Criteria (26,28,37,29–36), 21 with 2001 McDonald Criteria (38), 105 with 2005 Revised McDonald Criteria (25,39) and 300 with 2010 Revised McDonald Criteria (40–46). In addition, four populations of MS patients presented several diagnostic criteria, namely 29 patients were diagnosed with 2001 McDonald, 2005 Revised McDonald and 2010 Revised McDonald Criteria (47), 25 with 2001 McDonald and 2005 Revised McDonald Criteria (48), 25 with Poser Criteria plus MRI (49) and 30 with Poser and 2001 McDonald Criteria (24).

Nineteen studies referred the duration of MS in their patients: the highest value was present by Piras et al (32), with 13,8 ± 6,8 years and the lowest was by López-Gongora et al (43), with 15,2 ± 9,4 months. Regarding the course of MS, five studies – 149 patients – did not specify the type of MS their patients had (27,33,46,47,49).

In those that mentioned it – twenty-one articles –, relapsing-remitting course was the most frequent (695 patients), followed by secondary-progressive (121), primary-progressive (27), benign multiple sclerosis (19), clinically isolated syndrome (7) and relapsing-progressive (5). The remaining 5 patients had not the course of their disease defined yet.

Eight studies also described the usual medication of MS patients (29,31,39,40,42,43,45,48). According to those, 256 patients were under immunomodulatory treatment – 109 with interferon β (more specifically 57 with interferon β-1a and 14 with interferon β-1b), 27 with natalizumab, 22 with fingolimod, 13 with glatiramer acetate, 6 with teriflunomide, 4 with dimethyl fumarate, 30 with or interferon beta or glatiramer acetate and 45 with other agents – and 48 also were under treatment with other substances directed to other diseases – 16 with antidepressants, 6 with stimulants, 1 with carbamazepine, 1 with pregabalin, 1 with sildenafil and 23 with other agents not specified.

Several scales were considered in most of the articles included in this SRL (twenty-five of twenty-six articles) and compared with ERPs. Expanded Disability Status Scale (EDSS) was mentioned in twenty-four articles. Its average value was presented in twenty articles, which ranged from 0,87 ± 0,91 (43) to 4,92 ± 2,2 points (27). In the four articles left, Whelan et al (25) presented its median, Matas et al (31) the percentage and number of people included in several ranges of this scale and both Amato et al (47) and Magnié et al (24) the maximum limit that patients could have to be included in the study.

Regarding Cognitive Evaluation Scales, two studies compared ERPs with MMSE (27,46) and three evaluated MoCA (41,42,46). ACE has not been addressed in any of them. Six articles did not used any cognitive scales to evaluate cognitive impairment (26,28,31,34,35,49). Besides those mentioned in inclusion criteria, other cognitive scales were assessed in twenty articles, being Beck's Depression Inventory (BDI), PASAT and SDMT more frequent evaluated (present in 7, 7 and 5 articles, respectively). All cognitive scales approached are summarized in Table 25 in Appendix 3.

A) MMSE was evaluated in Honig et al (27) and in Zeng et al (46). In the first one, healthy controls obtained 29,5 ± 1 points and MS patients 27,3 ± 2,9 points, MS patients demonstrating significantly lower results (p=0,01). In the second one, MMSE was 29,77 ± 0,439 in healthy controls and 28,04 ± 2,05 in MS patients, although this comparison was not statistically significant.

B) As mentioned previously MoCA was assessed in three studies. In El-din et al (41) its results in healthy controls was 29 ± 0,8 points and in MS patients was 23,7 ± 3,6 points, demonstrating a statistically significant correlation (p=0,000). In Gedizlioglu et al (42) healthy controls obtained 26,8 ± 1,9 points, MS patients obtained 25,7 ± 2,2 at relapses and 27,2 ± 1,8 points at remission period. In this study only comparison between MoCA at relapses vs remission was statistically significant (p<0,001), which means that there was not a significant correlation between healthy controls and MS patients. In Zeng et al (46), it was 28,62 ± 1,89 in healthy controls and 21,0 ± 4,69 in MS patients, being this comparison statistically significant (p<0,05).

A summary table of studies characteristic is present in Table 26 (Appendix 4). In the following sections it will be presented the variation of amplitude and latency of all twenty-six articles included in our SRL, according to the respective ERP and stimulation modality.

3.2.1. Auditory P300

Auditory modality of P300 was assessed in eighteen articles, using mostly oddball paradigm (thirteen of them). In the remaining five, other auditory paradigms were used.

A) Reduced Amplitude Only

None of the eighteen articles that evaluated auditory P300 revealed a reduced amplitude, without any variation of other parameters.

B) Increased Latency Only

Six of eighteen articles using auditory modality demonstrated a prolonged latency only, without any relevant modifications of its amplitude.

1.) In Pokryszko-Dragan et al (38), P300 comparison of amplitudes between healthy controls and MS patients was not statistically relevant. Its latency was at Fz 314,47 ± 18,80 msec in healthy controls and 336,47 ± 27,25 msec in MS patients, with p=0,005; at Cz 315,68 ± 17,86 msec in healthy controls and 336,52 ± 26,28 msec in MS patients, with

p=0,006; and at Pz 320,15 ± 20,13 msec in healthy controls and 335,85 ± 32,03 msec in MS patients, with p=0,02, which demonstrated a relevant increase of this parameter in patients' group. All MS patients (100%) had worse results in TMT and 18 patients (90,5%) in AVLT, demonstrating cognitive dysfunction through neuropsychological testing, more specifically, reduced working and recent memory, attention, and cognitive flexibility. RRMS patients in this study demonstrated both moderate cognitive impairment and prolonged latency of P300.

2.) In another study by Pokryszko-Dragan et al (44), P300 amplitudes comparison between group of healthy controls and MS patients was not significant. P300 latency revealed an increase in MS patients when compared with healthy controls – at Fz it was 321,4 ± 22,4 msec in healthy controls and 339,4 ± 29,5 msec in MS patients, with p=0,0008; at Cz it was 322,6 ± 23,4 msec in healthy controls and 340,6 ± 30,0 msec in MS patients, with p=0,001; at Pz it was 325,6 ± 23,7 msec in healthy controls and 343,1 ± 30,0 msec in MS patients, with p=0,002. Neuropsychological testing was only applied to MS patients, divided in three subgroups according to their fatigue level. Authors found that P300 latency was independent of the relation between SDMT and PASAT and fatigue measures, suggesting that this ERP may be an index of cognitive impairment.

3.) In Vázquez-Marrufo et al (35), although P300 amplitude was reduced in MS patients compared with healthy controls, this difference was not statistically relevant. Its latency was 342 ± 21 msec in healthy controls, 363 ± 37 in RRMS (with p=0,044) and 370 ± 21 msec in BMS (with p=0,003), which revealed a significant increase in MS patients compared with healthy controls. Authors did not apply cognitive scales in this study.

4.) In Waliszewska-Prosól et al (45), P300 amplitude was not statistical relevant although it had an increase tendency. Its latency was at Fz 314,5 ± 20,3 msec in healthy controls and 338,4 ± 23,5 msec in MS patients, with p=0,0002; at Cz 315,6 ± 22,3 msec in healthy controls and 336,4 ± 23,9 in MS patients, with p=0,001; and at Pz 318,3 ± 23,4 msec in healthy controls and 338,6 ± 21,4 msec in MS patients, with p=0,001, which revealed a statistically relevant increase in MS patients compared with healthy controls. SDMT was performed in all patients, still it did not demonstrate a significantly relation with P300 latency or amplitude.

5.) Finally, in Whelan et al (25), comparison of P300 amplitude between healthy controls and MS patients was not significant. Parietal P300 latency was 340, 1 msec in healthy controls, 373,16 msec in RRMS patients and 416,08 msec in SPMS, with p=0,039, which

revealed a relevant increase in patients' group. PASAT was also assessed in MS patients demonstrating a significant correlation with P300 latency (at central and parietal sites).

Table 2 – Summary of P300 results using Auditory Oddball Paradigm demonstrating only an increased latency (without relevant modifications of its amplitude).

	Amp. (μV)	**Lat. (msec)**
Pokryszko-Dragan et al (38)	N. C.	↑
Pokryszko-Dragan et al (44)	N. C.	↑
Vázquez-Marrufo et al (35)	N. C.	↑
Waliszewska-Prosól et al (45)	N. C.	↑
Whelan et al (25)	N. C.	↑

(N. C. = No change)

6.) In Sundgren et al (39), using two-target paradigm (more precisely low pitch stimulation), P300 amplitude at Pz was 10,3 ± 4,5 μV in healthy controls and 10,6 ± 4,7 μV, although this increasing tendency was not statistically relevant. Its latency was 326,2 ± 13,3 msec in healthy controls and 338,7 ± 15,9 msec in MS patients, with p=0,002, which demonstrated a significant increase of this parameter in MS group compared with healthy controls. MS patients demonstrated cognitive impairment through mainly neuropsychological tests applied, except in Benton Visual Retention Test.

Table 3 – Summary of P300 results of Sundgren et al (39) using other Auditory Paradigms demonstrating only an increased latency (without relevant modification of its amplitude).

	Paradigm	**Amp. (μV)**	**Lat. (msec)**
Sundgren et al (39)	Two-target Paradigm	N. C.	↑

(N. C. = No change)

C) Reduced Amplitude and Increased Latency Simultaneously

Nine of eighteen articles using auditory modality demonstrated not only a reduction of P300 amplitude but also a prolonged latency.

1.) In Gedizlioglu et al (42), P300 amplitude was 20,3 ± 9,6 μV in healthy controls and 9,3 ± 4,2 μV in MS patients during remissions, that is significantly reduced (with p<0,001). Its latency was 295,5 ± 25,5 msec in healthy controls and 327,4 ± 39,5 msec at MS remissions, that is significantly increased (with p<0,007). Comparison of MoCA results between healthy controls and MS patients did not present a significant correlation (neither on remissions nor relapses). Neuropsychological testing with BRB-N demonstrated that 48,6% of MS patients during remission and 28,6% of healthy controls had cognitive dysfunction, being the difference between MS patients and healthy controls statistically relevant.

2.) In Gerschlager et al (29), P300 amplitude was 7,1 ± 9,6 μV in healthy controls and 2,3 ± 6,6 μV in MS patients and its latency was 374 ± 43 msec in healthy controls and 389 ± 47 msec in MS patients, that is, amplitude was reduced in MS patients and its latency was prolonged when compared with healthy controls, although these comparisons were not statistically relevant (neither on P300 amplitude nor its latency). Regarding neuropsychological testing, SRT (immediate), concentration endurance test, PASAT and verbal fluency test demonstrated a reduced punctuation obtained in these tests in MS patients, compared with healthy controls. Results of BDI showed an increase in MS patients, compared with healthy controls. Although these results were present in neuropsychological tests, no significant correlation was found between them and electrophysiological tests.

3.) In Honig et al (27), P300 amplitude comparison with healthy controls was significant (p=0,02) only at P3bp – 10,38 ± 0,86 μV in healthy controls and 7,89 ± 0,62 μV in MS patients. Its latency comparison with healthy controls was significant at P3a (p=0,005), P3b (p=0,0005) and P3bp (p=0,01), with values of the last being 341 ± 4 msec in healthy controls and 373 ± 8 msec in MS patients. 11 patients (35%) showed normal values of this ERP and 20 (65%) presented abnormalities, not only in its latency but also in its waveform and symmetry. 11 patients (35%) – which 4 only had changes in P300 latency (presented in this study as P3b) – demonstrated delayed latencies more than two standard-deviations, although it had only occurred in one healthy control (3%). Regarding neuropsychological testing, this study concludes that not only MMSE but also dementia score as evaluation instruments of cognitive dysfunction were relatively insensitive, being the last one a better discriminator. KCFS demonstrated a higher applicability and BIMCT showed no interest in assessing cognitive dysfunction in MS.

4.) In Li (49), P300 amplitude was 8,67 ± 3,86 μV in healthy controls and 4,28 ± 1,93 μV in MS patients, with p<0,01, and its latency was 353,21 ± 39,61 msec in healthy controls and 426,16 ± 52,39 msec in MS patients, with p<0,01, which demonstrated MS patients demonstrated a statistically significant reduced amplitude and an increased latency of this ERP, compared with healthy controls. P300 showed abnormalities in 13 (52%) MS patients (prolonged latencies and reduced amplitudes). No neuropsychological tests were assessed in this study.

5.) In Magnié et al (24), in study 1, the comparison between healthy controls and MS patients results was not statistically significant. However, in study 2, P300 amplitude was 11,21 ± 2,99 μV in healthy controls and 7,89 ± 4,03 μV in MS patients, with p<0,05, that is, it was a significant reduction in this parameter in MS group. Its latency was prolonged

in MS patients compared with healthy controls, with p<0,01. P300 parameters were correlated significantly with neuropsychological testing, particularly with Stroop Test, BRB-N and GBT, these being representative of attentional and memory disfunction.

6.) In Piras et al (32), P300 amplitude was significantly reduced in MS patients compared to healthy controls (p=0,021). Its latency was 324,4 ± 25,6 msec in healthy controls and 354,7 ± 21,1 msec in MS patients, with p=0,04, which revealed a significant increase in the group of patients. Relatively to neuropsychological tests, deterioration index (WAIS subtest) was present in 50% (six) of MS patients, and so authors considered the WAIS battery a suitable instrument to assess cognitive dysfunction.

7.) Finally, in Zeng et al (46) P300 amplitude was 25,86 ± 10,98 μV in healthy controls and 10,73 ± 4,87 μV in MS patients. Its latency was 308,15 ± 16,63 msec in healthy controls and 321,6 ± 25,83 msec in MS patients. P value was <0,05 in both cases. These P300 results of MS patients compared with healthy controls demonstrated significant reduced amplitude and a prolonged latency. Moreover, cognitive dysfunction was present in 24,1% of patient group according to MMSE and in 81,9% according to MoCA, although it is important to state that this group included not only MS but also other disorders of idiopathic inflammatory-demyelinating diseases (IIDDs) spectrum. Besides this, it became clear that there is a correlation between P300 parameters and MoCA in those disorders, being this more appropriate to cognitive function assessment than MMSE.

Table 4 – Summary of P300 results using Auditory Oddball Paradigm demonstrating and increased latency and a reduced amplitude simultaneously.

	Amp. (μV)	**Lat. (msec)**
Gedizlioglu et al (42)	↓	↑
Gerschlager et al (29)	↓	↑
Honig et al (27)	↓	↑
Li (49)	↓	↑
Magnié et al (24)	↓	↑
Piras et al (32)	↓	↑
Zeng et al (46)	↓	↑

8.) In El-din et al (41), P300 amplitude measured in right ear was 9,36 ± 4,0 μV in healthy controls and 4,43 ± 3,2 μV in MS patients and in left ear was 9,21 ± 4,2 μV in healthy controls and 4,37 ± 3,1 μV in MS patients, being p=0,000 in both cases. Its latency in right ear was 305,4 ± 28,8 msec in healthy controls and 348,8 ± 25,7 msec in MS patients and in the left was 301,2 ± 31,5 msec in healthy controls and 344,1 ± 27,6 msec in MS patients, being p=0,000 also in both cases. In other words, lower amplitudes and longer latencies

were verified in MS patients compared to healthy controls. In addition, cognitive impairment was present in 57,5% of MS patients, measured by different neuropsychological scales – MoCA, WMS-R, WCST, Bender-Gestalt Test – and by this ERP. Authors affirmed that greater the variation in P300 parameters, greater the cognitive impairment of MS patients.

9.) In Triantafyllou et al (34), P300 amplitude was 10,2 ± 3,7 μV in healthy controls and 7,8 ± 3,6 μV in MS patients (lower when EDSS ≥ 3), being $p<0,01$. Its latency was 317,8 ± 23,4 msec in healthy controls and 341,5 ± 41,7 msec in MS patients (higher when EDSS ≥ 3), being $p<0,01$. ERPs abnormalities presented demonstrated that MS patients had significantly reduced P300 amplitudes and prolonged latencies, when compared to healthy controls. No cognitive scales were addressed in this study.

Table 5 – Summary of P300 results using other Auditory Paradigms demonstrating an increased latency and a reduced amplitude simultaneously.

	Paradigm	**Amp. (μV)**	**Lat. (msec)**
El-din et al (41)	Non-specified	↓	↑
Triantafyllou et al (34)	Discrimination Paradigm	↓	↑

D) Others

1.) In López-Gongora et al (43), P300 – more specifically P3b – amplitude was 8,39 ± 4,00 μV in healthy controls and 8,95 ± 4,52 μV in MS patients. Its latency was 454 ± 69 msec in healthy controls and 464 ± 63 msec in MS patients. Although ERPs showed abnormalities in MS patients when compared with healthy controls (increased amplitude and latency), these were not statistically significant. Relatively to neuropsychological testing, there were no significant differences between healthy controls and MS patients, except for phonetic verbal fluency (parameter of BRB-N), where the last group perfomed worse.

Table 6 – Summary of P300 results of López-Gongora et al (43) using Auditory Oddball Paradigm without any relevant modification in both ERP parameters.

	Amp. (μV)	**Lat. (msec)**
López-Gongora et al (43)	N. C.	N. C.

(N. C. = No change)

2.) In Jung et al (30), using auditory passive oddball task, P300 – more specifically P3a – amplitude was not assessed. Its latency was 259 ± 20,3 msec in healthy controls and 249 ± 32,2 msec in MS patients, with $p=0,036$, which revealed a relevant increase in this parameter. In addition, MS patients had lower punctuation on MATTIS and the difference

between healthy controls and these patients in CVLT and PASAT was not significant. Using these neuropsychological test, 33,3% (six) MS patients demonstrated cognitive impairment and 66,7% (twelve) had a normal cognitive function. Relatively to the relation between these cognitive scales and P300, P3a was present in 83,4% (ten) of MS patients that had a normal cognitive function and in 50% (3) of those with cognitive impairment.

3.) In Matas et al (31), using tone burst stimulus, the P300 abnormality most found was longer latency in 75%, with more abnormal results in MS patients, although its comparison with healthy controls were not statistically significant (313,27 msec in healthy controls and 312,34 msec in MS patients). Neuropsychological testing was not approached in this study.

Table 7 – Summary of P300 results of the remaining studies using other Auditory Paradigms.

	Paradigm	**Amp. (μV)**	**Lat. (msec)**
Jung et al (30)	Passive Oddball Task	_____	↓
Matas et al (31)	Tone Burst Stimulus	_____	N. C.

(N. C. = No change)

3.2.2. Visual P300

Visual P300 was mentioned in eleven articles, obtained through oddball paradigm in six of them (24,25,28,32,37,40). Five remaining articles evaluated visual P300 using other paradigms.

A) Reduced Amplitude Only

Three of eleven articles using visual modality demonstrated only a reduced amplitude, without any relevant modifications of its latency.

1.) In Whelan et al (25), parietal P300 amplitude was 4,74 μV in healthy controls, 2,63 μV in RRMS patients and 2,64 μV in SPMS, that is, was reduced in MS patients when compared with healthy controls, with p=0,001. Its parietal latency comparison with healthy controls did not show statistically significant results. Although PASAT results correlated significantly in auditory modality, the same was not verified in visual P300.

Table 8 – Summary of P300 results of Whelan et al (25) using Auditory Oddball Paradigm demonstrating a reduced amplitude only (without any relevant modification in its latency).

	Amp. (μV)	**Lat. (msec)**
Whelan et al (25)	↓	N. C.

(N. C. = No change)

2.) In Covey et al (48), using N-back Task – after participants memorized an item, a discrete stimuli is continuously presented while participants choose if the stimulus corresponded (or not) to the item showed in previous *n* trials –, P300 amplitude was reduced in MS patients compared to healthy controls (with p=0,024) whereas its latency did not show a significant difference between healthy controls and MS patients. In addition, mean results on PASAT and SDMT tend to be lower in MS patients, although the difference was not statistically relevant.

3.) In Vázquez-Marrufo et al (36), P300 amplitude was reduced in MS patients when compared with healthy controls, with p=0,002. Values of its latency were not presented. Moreover, MS patients demonstrated SDMT results of 2 standard deviation under the cut-off scores considered, which revealed an attentional deficit in these patients.

Table 9 – Summary of P300 results using other Visual Paradigms demonstrating only a reduced amplitude (without any relevant modification of its latency).

	Paradigm	**Amp. (μV)**	**Lat. (msec)**
Covey et al (48)	N-back Task	↓	N. C.
Vázquez-Marrufo et al (36)	Attention Network Test	↓	___

(N. C. = No change)

B) Increased Latency Only

Two of eleven articles using visual modality demonstrated only a prolonged latency, without any relevant modifications of its amplitude.

1.) In Ellger et al (28), P300 amplitude was 39 ± 20 μV and its latency was 470 ± 59 msec, being the last parameter compared with the normative values considered. This study showed a pathological increased in P300 latency in 36% of MS patients, higher than anticipated in the general population. This was also verified in EDSS values <3, demonstrating a cognitive decline even when physical impairment was minor. No cognitive scales were evaluated.

Table 10 – Summary of P300 results of Ellger et al (28) using Visual Oddball Paradigm demonstrating only an increased latency.

	Amp. (μV)	**Lat. (msec)**
Ellger et al (28)	____	↑

2.) In González-Rosa et al (26), P300 amplitude did not showed significant abnormalities between MS patients and healthy controls and its latency was prolonged when compared to healthy controls, with p=0,001. No cognitive scales were assessed in this study.

Table 11 – Summary of P300 results of Gonzalez-Rosa et al (26) using other Visual Paradigms demonstrating only an increased latency (without relevant modification of its amplitude).

	Paradigm	**Amp. (μV)**	**Lat. (msec)**
Gonzalez-Rosa et al (26)	Modified Posner Paradigm	N. C.	↑

(N. C. = No change)

C) Reduced Amplitude and Increased Latency Simultaneously

Four of eleven articles using visual modality demonstrated not only a reduction of P300 amplitude but also a prolonged latency.

1.) In Artemiadis et al (40), P300 amplitude results were 9,4 ± 3,11 μV in healthy controls and 6,75 ± 4,44 μV in MS patients, with p=0,01, that is, there was a reduction in the patients group. P300 latency obtained was 310,87 ± 16,6 msec in healthy controls and 345,31 ± 39,42 msec in MS patients, with p=0,001, that is, there was an increase in patients' group. In addition, 39 MS patients (67,2%) presented an abnormal P300 – 10 had abnormal amplitude and latency, 21 only abnormal latency and 8 abnormal amplitude – that is, patients had significantly lower P300 amplitudes and more increased latencies. Moreover, total cognitive score obtained through SDMT, CVLT-II and BVMT-R was reduced in MS patients when compared to healthy controls, being lower in those who demonstrated P300 abnormalities. This battery of neuropsychological testing (BICAMS) correlated significantly with P300. In the first scale, this reduction verified independently of P300 values, in the second it was demonstrated only in those with P300 abnormalities and in the last one it occurred mainly when P300 was abnormal. Finally, P300 amplitude and latency demonstrated a statistically significant correlation with all neuropsychologic tests, except for CVLT-II in the last parameter.

2.) In Magnié et al (24), in study one, P300 amplitude was reduced in the group with attentional assessment dysfunction compared to healthy controls and its latency was prolonged in the same group mentioned compared to healthy controls. In study two, P300 amplitude comparison with healthy controls was not statistically relevant and P300 latency was prolonged compared to healthy controls in both visual (p<0,05) and auditory (p<0,01) modalities. As mentioned earlier, P300 parameters correlated significantly with neuropsychological testing, mainly with Stroop Test, BRB-N and GBT, these being representative of not only attentional but also memory function.

3.) In Piras et al (32), P300 amplitude was significantly reduced in MS patients compared to healthy controls (p=0,041) and its latency was 353,1 ± 15,2 msec in healthy controls and 376,2 ± 25,4 msec in MS patients, with p=0,04, that is, significantly prolonged. As stated

above, deterioration index (WAIS subtest) was present in 50% (six) of MS patients, being WAIS battery a suitable instrument to assess cognitive dysfunction.

Table 12 – Summary of P300 results in studies using Visual Oddball Paradigm, demonstrating a reduced amplitude and an increased latency simultaneously.

	Amp. (μV)	**Lat. (msec)**
Artemiadis et al (40)	↓	↑
Magnié et al (24)	↓	↑
Piras et al (32)	↓	↑

4.) In Amato et al (47), P300 amplitude was reduced in the frontal patients (compared to healthy controls and to non-frontal patients) and its latency was delayed MS patients (compared to healthy controls), being p=0,000 and p=0,015, respectively. Neuropsychological testing was used to divided MS patients according to their performance in "frontal patients" and "non-frontal patients", being that classification related with ERPs latency.

Table 13 – Summary of P300 results of Amato et al (47) using other Visual Paradigms demonstrating a reduced amplitude and an increased latency simultaneously.

	Paradigm	**Amp. (μV)**	**Lat. (msec)**
Amato et al (47)	Stroop Task	↓	↑

D) Others

1.) In Vázquez-Marrufo et al (37), abnormalities in P300 amplitude and latency were not statistically relevant, although its latency showed an increase in MS patients with EDSS of 5 ± 0,91 points, compared to healthy controls and low-EDSS patients. According to neuropsychological testing – SDMT and PASAT – used in this study, it is possible to conclude that the higher the physical disability of MS patients provided by EDSS, higher the cognitive impairment. Low-EDSS patients demonstrated almost total cognitive functioning although moderate-EDSS showed reduced values when compared with the normative values considered.

Table 14 – Summary of P300 results of Vázquez-Marrufo et al (37) using Visual Oddball Paradigm with no modification of the ERPs parameters.

	Amp. (μV)	**Lat. (msec)**
Vázquez-Marrufo et al (37)	N. C.	N. C.

(N. C. = No change)

2.) In Sundgren et al (39), P300 amplitude was increased in MS patients compared with healthy controls, with p<0,03, and its latency comparison with control group was not

significant statistically. As mentioned above, MS patients demonstrated cognitive impairment through mainly neuropsychological tests applied, except in Benton Visual Retention Test.

Table 15 – Summary of P300 results of Sundgren et al (39) using other Visual Paradigms with an increased amplitude.

	Paradigm	**Amp. (μV)**	**Lat. (msec)**
Sundgren et al (39)	Kanizsa illusory images	↑	N. C.

(N. C. = No change)

3.2.3. N400

This ERP was only evaluated in Amato et al (47), using Visual Stroop Task. Its amplitude showed a reduction in frontal patients (compared to healthy controls and non-frontal patients). Its latency was delayed in frontal patients (compared to healthy controls and non-frontal group). All comparisons were statistically significant. As mentioned earlier, neuropsychological tests used in this study had the purpose of divide MS patients according to their performance in "frontal patients" and "non-frontal patients", what proved to be significantly related with ERPs latency.

Table 16 – Summary of N400 results of Amato et al (47) using Visual Stroop Task.

	Paradigm	**Amp. (μV)**	**Lat. (msec)**
Amato et al (47)	Visual Stroop Task	↓	↑

3.2.4. MMN

This ERP was assessed in two studies (30,33), both using auditory paradigms.

1.) In Jung et al (30), MMN area was 123 ± 59,3 μV msec in healthy controls and 78 ± 47,5 μV msec in MS patients, with p=0,001, which demonstrated a significant reduction in this parameter, abnormality found in several patients in early phases of MS. Its latency also showed a relevant reduction, being 172 ± 20,5 msec in healthy controls and 160 ± 28,3 msec in MS patients, with p=0,005. As mentioned earlier, MS patients demonstrated lower punctuation on MATTIS and the difference between healthy controls and these patients in CVLT and PASAT was not relevant. According to these neuropsychological tests, 33,3% (six) MS patients demonstrated cognitive impairment and 66,7% (twelve) had a normal cognitive function globally. Relatively to the relation between these cognitive scales and MMN, it was detected in 93,7% (eleven) of MS patients with a normal cognitive function and 83,4% (five) of those with cognitive impairment. In MS patients with

cognitive impairment, MMN area was half of the one verified in MS patients with a preserved cognitive function.

Table 17 – Summary of MMN area and latency results of Jung et al (30).

	Paradigm	Area (µV msec)	Lat. (msec)
Jung et al (30)	Auditory Passive Oddball Task	↓	↓

2.) In Santos et al (33), the comparison between MS patients with healthy controls in both MMN amplitude and latency was not statistically relevant, although this ERPs was present in 60% of MS patients with duration variation protocol and in 45% of them with frequency variation. The authors found a significant relation between the lack of MMN wave and cognitive dysfunction, being that 57,5% of MS patients showed abnormalities in Cognitive Evaluation Scales (PASAT).

Table 18 – Summary of MMN amplitude and latency results of Santos et al (33) and its presence during duration and frequency variation protocol.

	Paradigm	Amp. (µV)	Lat. (msec)	D. V.	F. V.
Santos et al (33)	Auditory	N. C.	N. C.	Present in 60%	Present in 45%

(N. C. = No change; D.V. = Duration Variation Protocol; F. V. = Frequency Variation Protocol)

3.3. Risk of Bias

By the application of ROBINS-I Tool resulted the following graphic (Figure 2) demonstrating the percentage of each bias in all twenty-six articles and Figure 3 discriminating our judgment of each domain determining the risk of bias in each article.

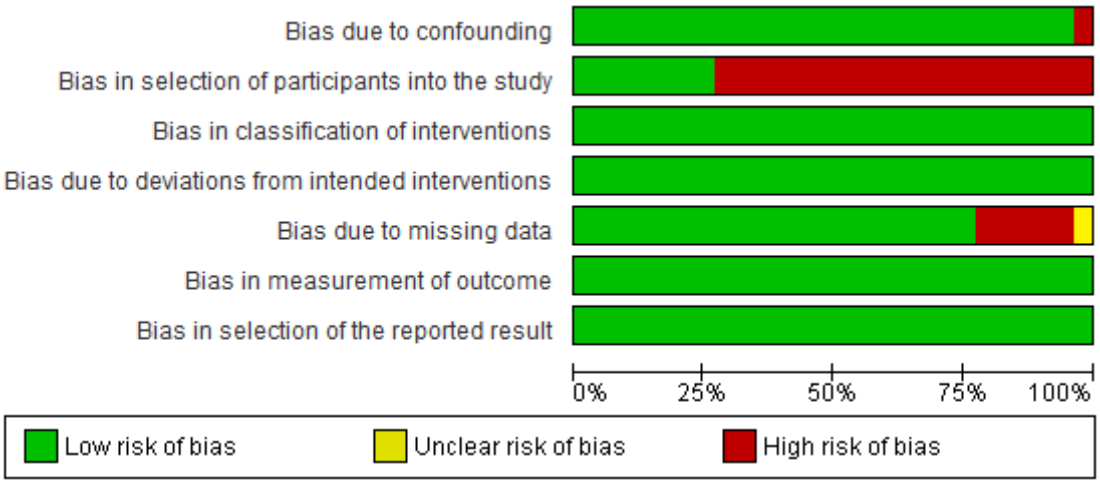

Figure 2 – Risk of Bias graphic.

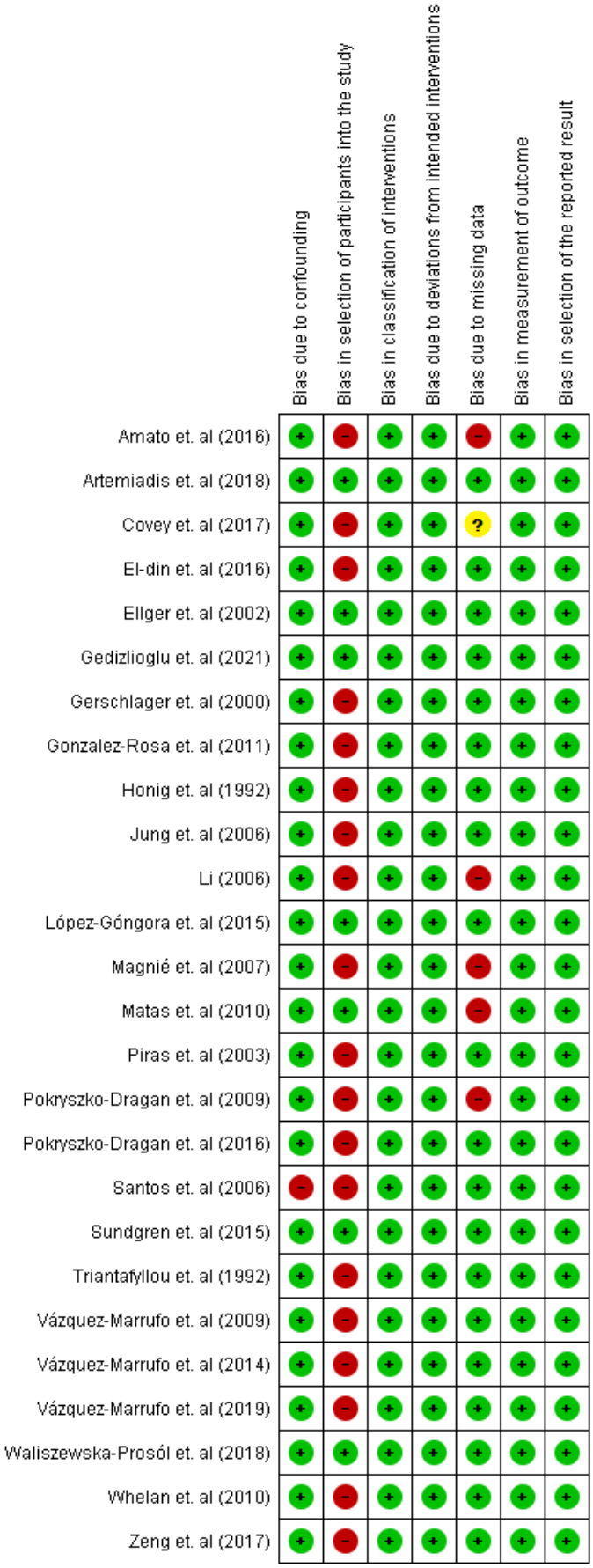

Figure 3 – Risk of Bias summary.

3.4. Quality Assessment

After applying the questions to each article, overall appraisal was optimistic, since all twenty-six articles were included. Inclusively, two articles demonstrated all the necessary characteristics to classify a study as maximum quality (28,48). Three questions lead mainly to a negative or to an unclear appreciation, namely Question 1 (*Were the criteria for inclusion in the sample clearly defined?), 5 (Were confounding factors identified?) and 6 (Were strategies to deal with confounding factors stated?)*. Table 27 (in Appendix 5) demonstrate the answers to the checklist that evaluated the quality of each study according to JBI Critical Appraisal Tools.

4. Discussion

4.1. Summary of Results

P300 was the most discussed ERP, being present in twenty-five of twenty-six articles. P300 demonstrated a reduced amplitude or an increased latency in 84% of the studies where this ERP were included (twenty-one of twenty-five). Of those where P300 abnormalities were verified, 57% had variation of P300 parameters simultaneously (twelve of twenty-one). In nineteen studies of those that included P300, this ERP was compared with Cognitive Scales – two used MMSE (27,46), three MoCA (41,42,46) and nineteen studies used other scales. In those twenty-five articles that approached P300, eighteen obtained it through an auditory modality, eleven through a visual one and four through both.

Auditory P300 amplitude was reduced in nine studies (24,27,29,32,34,41,42,46,49), had no statistically significant results in seven studies (24,25,35,38,39,43–45) and it was not mentioned in two articles (30,31). Its latency was increased in fifteen studies (24,25,42,44–46,49,27,29,32,34,35,38,39,41), had no significant results in two (31,43) and it was reduced in one (30). Of those eighteen studies that used auditory modality, eight did not showed any change of at least one of the parameters (amplitude or latency).

Visual P300 amplitude demonstrated a reduction in seven studies (24,25,32,36,40,47,48), had no significant results in two (26,37), showed an increase in one (39) and was not approach in another (28). Its latency was prolonged in six studies (24,26,28,32,40,47), had no significant results in four (25,37,39,48) and was not mentioned in one (36). Of those eleven studies that used a visual modality, five did not revealed any change of at least one of the parameters (amplitude or latency).

N400 was evaluated in one article (47), using a visual stimulation. Cognitive Scales were used as comparison – Stroop test, Tower of Hanoi, dual task, WCST, verbal fluency tests – but did not include MMSE or MoCA or ACE. In this study, amplitude was reduced, and latency increased.

MMN was assessed in two articles (30,33), obtained through an auditory stimulation. Cognitive Scales were also applied to comparison but none of them were mentioned in Inclusion Criteria. In one of them (30), both its area and its latency was reduced. In (33), neither amplitude or latency revealed any relevant variation.

4.2. Outcomes

4.2.1. Auditory P300

A reduction of its amplitude and an increase of its latency simultaneously was present in nine of eighteen them, that is, in 50% of included studies. In six of the remaining nine studies its latency was increased, and so the variation of this parameter is verified in 83,3% of eighteen articles.

Only one study (30) demonstrated an unexpected outcome – a reduced latency. This difference could be related to separation of P300 wave in P3a and P3b. Authors suggest that P3b is correlated with auditory information processing and P3a with automatical and pre-attentive information processing (along with MMN) (30). Since the paradigm used to obtain the auditory P300 in this study was non-conventional – passive oddball task –, the results should not be valued and compared with other studies.

Although the relation between auditory P300 abnormalities and cognitive impairment in MS is well established in scientific literature, we believe it is crucial for the purpose of this SRL to understand if this ERP (auditory P300) is more suitable to detect this clinical manifestation in MS patients than neuropsychological testing. For the data to be more comparable and since oddball paradigm is frequently used in research (14), we decided to analyze and to evidence the relation mentioned above in studies that used this paradigm to obtain P300, that demonstrated a reduced amplitude or an increased latency and that compared it with neuropsychological testing.

Gedizlioglu et al (42) concluded that MS patients may present a reversible reduction in cognitive function during relapses. Although that comparison is beyond the objectives of this SRL, authors (42) suggested that P300 may be an index of this impairment because of its practicability and repeatability.

Pokryszko-Dragan et al (44) – in a study published in 2016 – suggested that P300 may be a more proper method to evaluate cognitive function than cognitive scales that assess cognition by domains, since it is more precise and gives information about cognitive impairment globally. It is noteworthy that Pokryszko-Dragan et al (38) – in a study published in 2009 – defended that neuropsychological testing was more suitable for continuous assessment of cognitive function in MS patients than ERPs, being these a complementary tool only. These differences are the prove that ERPs are becoming increasingly relevant regarding cognitive performance in MS and its assessment in clinical practice.

Waliszewska-Prosól et al (45) hypothesized that auditory P300 may be an index of subtle cognitive impairment, since all patients obtained normal results in SDMT, which demonstrate that, according to neuropsychological testing, they were not significantly cognitively impaired, although P300 abnormalities demonstrated.

Zeng et al (46) confirmed the existence of a relation between P300 parameters (both amplitude and latency) and MoCA not only in MS but also in other idiopathic inflammatory-demyelinating diseases. Besides this, authors emphasized not only the relevance of P300 assessment in research of cognitive impairment but also its utility as a complementary tool in clinical practice.

Finally, Magnié et al (24) and Piras et al (32) evaluated both auditory and visual P300, so their studies will be approached in the next section (4.2.2 Visual P300).

4.2.2. Visual P300

In this modality of P300 studies revealed less differentiated results. Four of eleven studies revealed a reduction of its amplitude and an increase of its latency simultaneously (36,4%). Of the remaining seven studies, three demonstrated only a reduced amplitude (42,9%) and two a prolonged latency (28,6%). In total, visual P300 amplitude was reduced in 63,6% studies and its latency was increased in 54,4%.

Also only one study (39) revealed a different outcome – an increased amplitude. Authors proposed that because patients demonstrated cognitive impairment and an increased in P300 amplitude in frontal location, the variation of this parameter was not due to cognitive dysfunction and could be a sign of compensatory brain mechanisms using to diminished cognitive impairment (39). It is noteworthy that Kanizsa illusory images (square and non-square) were applied in this study to obtain visual P300, which is not the paradigm used most often (14).

As mentioned above, we consider that – according to the objective of our SRL – it is necessary to understand if this ERP (visual P300) can be a more relevant diagnosis tool of cognitive impairment in MS than neuropsychological testing. As done in the previous section (4.2.1. Auditory P300), the following studies meet the mentioned requirements (P300 obtained using oddball paradigm, demonstrating a reduced amplitude or an increased latency, and compared it with neuropsychological testing).

According to Artemiadis et al (40), P300 correlated significantly with BICAMS battery, which sustained the idea that P300 is an indicator of cognitive function. Besides this, MS

patients with P300 abnormalities demonstrated lower scores on BVMT-R than patients with normal P300 parameters.

Magnié et al (24) suggested that P300 abnormalities in visual modality precede those in verified in auditory modality, and both occurred previously to changes in neuropsychological testing. Besides this, authors (24) also concluded that P300 amplitude and latency in both modalities correlated significantly with cognitive scales. Moreover, Magnié et al (24) reinforced the need to implement ERPs as a complementary tool in clinical practice not only for diagnose cognitive impairment in MS but also to follow-up this clinical manifestation, before it manifests through cognitive scales.

Piras et al (32) provided a different perspective of P300 utility in clinical practice to diagnose cognitive impairment in MS. Authors (32) defended that ERPs may be a useful method to assess cognitive function when physical disability becomes a barrier to apply cognitive scales.

4.2.3. N400

The only study included approached this ERP was perfomed by Amato et al (47) and revealed a reduction of its amplitude and an increase of its latency. Several authors suggest that N400 obtained by that specific paradigm (Stroop-Task) is a consequence of anterior cingulate activity (50) that had important functions on conflict monitoring and on compensatory adjustment in cognitive control (51–53). As an indicator semantic memory access, Milosevic et al (54) suggested that this ERP could be a method to evaluate this characteristic in Multiple Sclerosis.

Since only this study evaluated N400 in our SRL, it is not reasonable to assume its applicability as a diagnostic tool of cognitive dysfunction in MS. More studies are needed to confirm its relevance alone in this clinical manifestation.

4.2.4. MMN

MMN was the ERP with more discrepancies in results of the two articles included in our SRL.

Besides MMN latency, Jung et al (30) analyzed its area, not its amplitude *per si*, arguing that this approach in this specific ERP was more reproducible (55). Authors defined this parameter as “the area under the curve computed between the onset and the offset” of MMN wave. This parameter was reduced along with MMN latency. Authors suggest that

these variations resulted from abnormalities in components that originate this ERP. Latency variation was not emphasized, and it was suggested more studies, resorting to topographical mapping and evaluation of MRI lesions in order to understand which specific neural component was altered in MS. Authors (30) suggested that variation in MMN parameters – along with P300 (also evaluated in this study) – may indicate a slight cognitive impairment in a pre-clinical period.

In the second article, Santos et al (33) did not obtained amplitude or latency abnormalities although interesting results were found. MMN was present in 60% of MS patients with duration variation protocol and in 45% with frequency variation, which means it was absent in 40% and in 55% respectively. As mentioned above, this study compared its ERPs results with several Cognitive Scales, such as PASAT. Authors found that cognitive impairment stated by PASAT is correlated with MMN absence.

Since only two articles considered this ERP and their results were discrepant, it is not acceptable to infer its importance as a tool of diagnosis in cognitive dysfunction in MS. More studies are needed before its application on clinical practice with this purpose.

4.3. Limitations

Our SRL was not free of some limitations: a) small sample size, considering the worldwide prevalence of MS, b) unavailability of data about MMSE, MoCA and ACE in several included articles, c) lack of responses from several authors contacted, d) impossibility to analyze the data required to authors, e) lack of more concrete data about MS patients with or without cognitive impairment and which of them revealed variation of ERPs parameters included.

5. Conclusion

The majority of MS patients with cognitive dysfunction demonstrated ERPs abnormalities – twenty-two of twenty-six studies demonstrated a reduced amplitude or an increased latency and twelve of those twenty-two had variation in both parameters simultaneously.

Findings of our SRL suggest that P300 may be an appropriate diagnostic method for cognitive impairment in MS revealing this manifestation earlier than through the application of cognitive scales. More studies are needed to understand the relevance of N400 and MMN to assess this manifestation in clinical practice.

Although MMSE, MoCA and ACE are the most used cognitive scales in clinical practice generally, they are not suitable to evaluate this manifestation in MS. There are several batteries and scales of neuropsychological testing more appropriate to assess and screen cognitive impairment in this specific disease, such as BRN-B, MACFIMS and BICAMS. ERPs may provide earlier data about cognitive function compared with standard neuropsychological tests, which applied systematically may have a significant impact in improving quality of life of MS patients.

More studies comparing MS patients with standard cognitive scales – MMSE, MoCA and ACE – and these ERPs are required to implement those permanently in clinical approach of cognitive function in MS and not only as an alternative method. Besides this, it would also be important for this field a systematic review similar to the one developed but including only studies with amplitude and latency variation simultaneously and using more suitable and validated cognitive scales to evaluated cognitive function in MS. Finally, it would also be relevant to understand which P300 modality – auditory or visual – is more relatable and provide earlier results when cognitive impairment is present in MS – studies with both modalities in the same group of patients would be useful.

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Appendix

Appendix 1 – MS Diagnosis Criteria included in this SRL

Table 19 – Schumacher Criteria 1965 (Adapted from (56)):

Clinical Criteria	. Signs of dysfunction of the CNS (abnormalities on neurological exam). . Involvement of 2 or more separate parts of de CNS. . Involvement mostly of white matter – signs of optic nerve, cerebral subcortical, corticobulbar, corticospinal, medial longitudinal fasciculus, cerebellar subcortical, spinocerebellar, and long sensory tract dysfunction. . Patterns of involvement of the neuroaxis: 2 or more episodes of worsening (during at least 24 hours, separated by 1 month or more) or slow/stepwise progression during at least 6 months. . Onset at 10-50 years (inclusive). . Absence of a better explanation to the signs and symptoms of the patient – decision must be made by a physician competent in clinical neurology.

Table 20 – Poser Criteria 1983 (Adapted from (57)):

Category	**Attacks**	**Number of Separate Lesions**		**Oligoclonal bands/increased IgG on CSF**
		Clinical Evidence	**Paraclinical Evidence**	
Clinical definite	A1: 2 A2: 2	A1: 2 A2:1 and	A2: 1	
Laboratory-supported definite	B1: 2 B2: 1 B3: 1	B1: 1 or B2: 2 B3:1 and	B1: 1 B3: 1	B1: + B2: + B3: +
Clinically probable	C1: 2 C2: 1 C3: 1	C1: 1 C2: 2 C3:1 and	 C3: 1	
Laboratory-supported probable	D1: 2			D1: +

Table 21 – 2001 McDonald Criteria (Adapted from (58)):

Clinical Presentation	**Additional Data Needed for MS Diagnosis**
2 or more attacks Objective clinical evidence of 2 or more lesions	None[a]
2 or more attacks Objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by MRI[b] or 2 or more lesions detected in MRI consistent with MS + positive CSF[c]

	or Await further clinical attack implicating a different site
1 attack Objective clinical evidence of 2 or more lesions	Dissemination in time, demonstrated by MRI[d] or Second clinical attack
1 attack Objective clinical evidence of 1 lesion Monosymptomatic presentation/ clinically isolated syndrome	Dissemination in space, demonstrated by MRI[b] or 2 or more lesions detected in MRI consistent with MS + positive CSF[c] and Dissemination in time, demonstrated by MRI[d] or Second clinical attack
Insidious neurological progression suggestive of MS	Positive CSF[c] and Dissemination in space, demonstrated by 1. 9 or more T2 lesions in brain or 2. 2 or more lesions in spinal cord or 3. 4-8 brain + 1 spinal cord lesion or Abnormal VEP[e] associated with 4-8 brain lesions or with <4 brain + 1 spinal cord lesion demonstrated by MRI and Dissemination in time, demonstrated by MRI[d] or Continued progression for 1 year

All criteria are request to the diagnose of MS. If not completely fulfilled, the diagnosis is "possible MS". If the criteria are explored but not fulfilled, the diagnosis is "not MS".

[a] No additional tests required, but if MRI or CSF analysis are undertaken and negative, alternative diagnosis must be considered (there must be no better explanation for the signs and symptoms of the patient).

[b] Criteria of MRI demonstrating space dissemination (MRI Criteria for Brain Abnormality from (59) and (60):

Three of four of the following:

One gadolinium-enhancing lesion or 9 T2 hyperintense lesions if there is no gadolinium-enhancing lesion;

At least 1 infratentorial lesion;

At least 1 juxtacortical lesion;

At least 3 periventricular lesions.

Note: one spinal cord lesion can substitute for one brain lesion.

[c] Positive CSF – oligoclonal bands (detected by established methods) different from any such bands in serum or raised IgG index in cerebrospinal fluid

[d] Criteria of MRI demonstrating time dissemination:

First scan in 3 or more months after the onset of the clinical event:

1 gadolinium-enhancing lesion is sufficient to demonstrate dissemination in time;

If there is no enhancing lesions, a follow-up scan is necessary – 3 months are recommend → a new T2 or gadolinium-enhancing lesion met the criteria for dissemination in time.

First scan in less than 3 months after the onset of the clinical event:

New gadolinium-enhancing lesion on a second scan 3 or more months after the onset of the clinical event demonstrates dissemination in time;

No enhancing lesion in a second scan, a further scan not less than 3 months after the first scan that shows T2 lesions or and enhancing lesion is sufficient to demonstrate dissemination in time.

[e] Abnormal visual evoked potential of the type seen in MS – delay with a well-preserved wave form. (61)

Table 22 – 2005 Revised McDonald Criteria Revised (Adapted from (62)):

Clinical Presentation	Additional Data Needed for MS Diagnosis
2 or more attacks[a] Objective clinical evidence of 2 or more lesions	None[b]
2 or more attacks[a] Objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by MRI[c] or 2 or more lesions detected in MRI consistent with MS + positive CSF[d] or Await further clinical attack[a] implicating a different site
1 attack[a] Objective clinical evidence of 2 or more lesions	Dissemination in time, demonstrated by MRI[c] or Second clinical attack[a]
1 attack[a] Objective clinical evidence of 1 lesion Monosymptomatic presentation/ clinically isolated syndrome	Dissemination in space, demonstrated by MRI[c] or 2 or more lesions detected in MRI consistent with MS + positive CSF[d] and Dissemination in time, demonstrated by MRI[c] or Second clinical attack[a]
Insidious neurological progression suggestive of MS	One year of disease progression (retrospectively or prospectively determined) and 2 of the following: a. Positive brain MRI (9 T2 lesions or 4 or more T2 lesions with positive VEP)[f] b. Positive spinal cord MRI (2 focal T2 lesions) c. Positive CSF[d]

If the criteria indicated are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is MS; if the criteria are not totally met but it is suspicious, the diagnosis is "possible MS"; if during the evaluation another diagnosis comes up that better explains the entire clinical course, then the diagnosis is "not MS".

[a] Attack – an episode of neurological disturbance for which causative lesions are likely to be inflammatory or demyelinating in nature; there should be subjective report (with objective findings) or objective observation that the event lasts for at least 24 hours. (58)

[b] No additional tests required, but if MRI or CSF analysis are undertaken and negative, alternative diagnosis must be considered (there must be no better explanation for the signs and symptoms of the patient).

[c] Criteria of MRI demonstrating space dissemination (MRI Criteria for Brain Abnormality from (59) and (60):

Three of four of the following:

One gadolinium-enhancing lesion or 9 T2 hyperintense lesions if there is no gadolinium-enhancing lesion;

At least 1 infratentorial lesion;

At least 1 juxtacortical lesion;

At least 3 periventricular lesions.

Note: one spinal cord lesion can be considered equivalent to a brain infratentorial lesion: an enhancing spinal cord lesion is considered to be equivalent to an enhancing brain lesion, and individual spinal cord lesion can contribute together with individual brain lesions to reach the required number of T2 lesions.

[d] Positive CSF – oligoclonal bands (detected by established methods) different from any such bands in serum or raised IgG index in cerebrospinal fluid.

[e] Criteria of MRI demonstrating time dissemination:

Two ways of showing dissemination in time through imaging:

Detection of gadolinium enhancement at least 3 months after the onset of the initial clinical event, if not at the site corresponding to the initial event

Detection of a new T2 lesion if it appears at any time compared with a reference scan done at least 30 days after the onset of the initial clinical event

[f] Abnormal VEP of the type seen in MS. (61)

Table 23 – 2010 Revised McDonald Criteria (Adapted from (63)):

Clinical Presentation	Additional Data Needed for MS Diagnosis
2 or more attacks[a] Objective clinical evidence of 2 or more lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack[b]	None[c]
2 or more attacks[a] Objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by: 1 or more T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial or spinal cord)[d] or Await further clinical attack[a] implicating a different CNS site
1 attack[a] Objective clinical evidence of 2 or more lesions	Dissemination in time, demonstrated by: Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan or Await a second clinical attack[a]
1 attack[a] Objective clinical evidence of 1 lesion (clinically isolated syndrome)	Dissemination in space, demonstrated by: For DIS: 1 or more T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial or spinal cord)[d] or Await a second clinical attack[a] implicating a different CNS site And For DIT: Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan or Await a second clinical attack[a]

Insidious neurological progression suggestive of MS (PPMS)	One year of disease progression (retrospectively or prospectively determined) and 2 of the following [d]: a. Evidence for DIS in the brain based on 1 or more T2 lesions in the MS-characteristic (periventricular, juxtacortical or infratentorial) regions b. Evidence for DIS in the spinal cord based on 2 or more T2 lesions in the cord c. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

If the criteria indicated are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is MS; if the criteria are not totally met but it is suspicious, the diagnosis is "possible MS"; if during the evaluation another diagnosis comes up that better explains the entire clinical course, then the diagnosis is "not MS".

[a] Attack (relapse, exacerbation) – a patient-reported or objectively observed events typical of an acute inflammatory demyelinating event in the CNS, current or historical, with duration of at least 24 hours, in the absence of fever or infection; before a definite diagnosis of MS can be made, at least 1 attack must be corroborated by findings on neurological examination, visual evoked potential response in patients reporting prior visual disturbance or MRI consistent with demyelination in the are of the CNS implicated in the historical report of neurological symptoms.

[b] Clinical diagnosis based on objective neurological findings for 2 attack is most secure.

[c] No additional tests are required, but if MRI or CSF analysis are undertaken and negative, alternative diagnosis must be considered (there must be no better explanation for the signs and symptoms of the patient).

[d] Gadolinium-enhancing lesions are not required; symptomatic lesions are excluded from consideration in subjects with brainstem or spinal cord syndromes.

Table 24 – 2017 Revised McDonald Criteria revised (Adapted from (6)):

Clinical Presentation	**Additional Data Needed for MS Diagnosis**
2 or more clinical attacks[a] Objective clinical evidence of 2 or more lesions or objective clinical evidence of 1 lesion as well as clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical lesion[b]	None[c]
2 or more clinical attacks[a] Objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by an additional clinical attack[a] implicating a different CNS site or by MRI[d]
1 clinical attack[a] Objective clinical evidence of 2 or more lesions	Dissemination in time, demonstrated by and additional clinical attack[a] or by MRI[d] OR demonstration of CSF-specific oligoclonal bands[e]
1 clinical attack[a] Objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by an additional clinical attack[a] implicating a different CNS site or by MRI[d] Dissemination in time, demonstrated by and additional clinical attack[a] or by MRI[d] OR demonstration of CSF-specific oligoclonal bands[e]
Insidious neurological progression suggestive of MS (PPMS)	PPMS can be diagnosed in patients with 1 year of disability progression (retrospectively or prospectively determined) independent of clinical relapse plus 2 of the following: a. One or more T2-hyperintense lesions – no distinction between symptomatic and asymptomatic

	– characteristic of MS in one or more of the following brain regions: periventricular, cortical or juxtacortical, or infratentorial b. 2 or more T2-hyperintense lesions – no distinction between symptomatic and asymptomatic – in the spinal cord c. Presence of CSF-specific oligoclonal bands

If the criteria indicated are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is MS; if the criteria are not totally met but it is suspicious, the diagnosis is "possible MS"; if during the evaluation another diagnosis comes up that better explains the entire clinical course, then the diagnosis is "not MS".

[a] Attack – equals to relapse, exacerbation and (when it is the first episode) clinically isolated syndrome.

[b] Clinical diagnosis based on objective clinical finding for 2 attacks is most secure; at least 1 attack, however, must be supported by objective findings.

[c] No additional tests are required; unless MRI is not possible, brain MRI should be obtained in all patients in whom the diagnosis of MS is being considered; spinal cord MRI or CSF examination should be considered in patients with insufficient clinical and MRI evidence supporting MS, with a presentation other than a typical clinically isolated syndrome, or with atypical features; if MRI or CSF analysis are undertaken and negative, alternative diagnosis must be considered (there must be no better explanation for the signs and symptoms of the patient).

[d] Demonstration of dissemination in space and time by MRI in a patient with clinically isolated syndrome:

In space: 1 or more T2-hyperintense lesions – no distinction between symptomatic and asymptomatic – that are characteristic of MS in 2 or more of 4 areas of the CNS: periventricular, cortical (for some patients – older than 50 year or those with vascular risk factors) or juxtacortical, and infratentorial brain regions, and the spinal cord.

In time: simultaneous presence of gadolinium-enhancing and non-enhancing lesions – no distinction between symptomatic and asymptomatic – at any time or by a new T2-hyperintense or gadolinium-enhancing lesion on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI.

[e] The presence of CSF-specific oligoclonal bands does not demonstrate dissemination in time per se but can substitute for the requirement for demonstration of this measure.

Appendix 2 – Database Search Strategy

PubMed – (((((("Multiple Sclerosis"[Mesh]) OR ("Multiple Sclerosis, Relapsing-Remitting"[Mesh])) OR ("Multiple Sclerosis, Chronic Progressive"[Mesh])) OR ("multiple sclerosis")) AND (((((("event-related potential*") OR ("event related potential*")) OR ("mismatch negativity")) OR (N400)) OR ("Event-Related Potentials, P300"[Mesh]))) AND ((("cogniti*") OR ("Neurocognitive Disorders"[Mesh])) OR ("Cognition"[Mesh])), which resulted in 68 articles.

Embase – (('multiple sclerosis'/exp) OR (multiple sclerosis)) AND (('event related potential'/exp) OR (event AND related AND potential*) OR ('mismatch negativity'/exp) OR ('n400'/exp) OR ('p300'/exp)) AND ((cogniti*) OR ('disorders of higher cerebral function'/exp) OR ('cognition'/exp)), which resulted in 207 articles.

Scielo – ("cognition" or "Neurocognitive Disorders" or "cognitive") [All indexes] and "multiple sclerosis" [All indexes] and ("event-related potentials" or "event related potentials" or p300 or n400 or "mismatch negativity") [All indexes], which resulted in 0 articles.

Web Of Science – (("Neurocognitive Disorders") OR ("cogniti*")) AND ((P300) OR (N400) OR ("mismatch negativity") OR ("event related potential*")) AND (("Multiple Sclerosis")), which resulted in 149 articles.

Appendix 3 – Cognitive Evaluation Scales

Table 25 – Summary of Cognitive Evaluation Scales presence and its respective article.

	Number of Articles	**Reference**
10/36 SR	1	(24)
AVLT	1	(38)
BDI	7	(29,36,37,39,42,43,48)
BIMCT	1	(27)
BMT	1	(24)
BRB-N	3	(24,42,43)
BRNBT	1	(44)
BVMT-R	1	(40)
BVRT	1	(39)
CET	1	(29)
Corsi Span	1	(32)
COWAT	1	(39)
CVLT	2	(30,40)
DI	1	(32)
Dementia Score	1	(27)
Digit Span Test	1	(39)
D-type Scale	1	(45)
Dual Task	1	(47)
EHI	1	(32)
FSS	3	(39,43,44)
GBT	1	(24)
HADS	1	(46)
HRS	1	(32)
KCFS	1	(27)
MATTIS	1	(30)
MFIS	1	(44)
MMSE	**2**	**(27,46)**
MoCA	**3**	**(41,42,46)**
MSFC	1	(33)
MSQoL-54	1	(42)
MSSS	3	(39,43,44)
NART	1	(48)
PASAT	7	(24,25,30,33,36,37,48)
Phasic alert	1	(30)
PSS	1	(45)
RPCM	1	(32)
SDMT	5	(36,37,40,45,48)
Snellen Charts	1	(39)
SRT	2	(24,29)
Stroop Test	2	(24,47)

TMT	3	(24,38,39)
Tower of Hanoi	1	(47)
Verbal Fluency Tests	2	(29,47)
Verbal Supraspan	1	(32)
VSS	1	(32)
VST	1	(32)
WAIS	3	(24,32,38)
WCST	2	(41,47)
WMS	1	(41)

Appendix 4 – Summary of Study Characteristics

Table 26 – Summary of Study Characteristics included in this SRL.

Authors	Year	N	Cognitive Scales	ERP	Amp. (μV)	Lat. (msec)
Amato et al (47)	2016	29	Stroop test Tower of Hanoi Dual task WCST Verbal fluency tests	P300	↓	↑
				N400	↓	↑
Artemiadis et al (40)	2018	58	SDMT CVLT-II BVMT-R Total cognitive score	P300	↓	↑
Covey et.al (48)	2017	25	NART BDI-II PASAT (2s and 3s) SDMT	P300	↓	N. C.
El-din et al (41)	2016	40	**MoCA** WMS-R WCST Bender-Gestalt test	P300	↓	↑
Ellger et al (28)	2002	179	-	P300	-	↑
Gedizlioglu et al (42)	2021	35	**MoCA** BRB-N BDI-II MSQoL-54	P300	↓	↑
Gerschlager et al (29)	2000	14	SRT CET Verbal fluency test BDI	P300	↓	↑
Gonzalez-Rosa et al (26)	2011	27	-	P300	N. C.	↑
Honig et al (27)	1992	31	**MMSE** Dementia Score BIMCT KCFS	P300	↓	↑
Jung et al (30)	2006	46	MATTIS CVLT Phasic alert PASAT (3s)	P300	-	↓
				MMN	-	↓
Li (49)	2006	25	-	P300	↓	↑
López-Góngora et al (43)	2015	27	MSSS BRB-N BDI FSS	P300	N. C.	N. C.
Magnié et al (24)	2007	30	PASAT BRB-N Stroop test TMT SRT 10/36 SR GBT BNT WAIS-R	P300	↓	↑
Matas et al (31)	2010	25	-	P300	-	N. C.

Piras et al (32)	2003	12	HRS EHI WAIS RPCM DI VST Corsi Span Verbal Supraspan VSS	P300	↓	↑
Pokryszko-Dragan et al (38)	2009	21	WAIS-R AVLT 1 and 2 TMT	P300	N. C.	↑
Pokryszko-Dragan et al (44)	2016	86	MSSS FSS MFIS BRBNT	P300	N. C.	↑
Santos et al (33)	2006	40	MSFC PASAT (3s)	MMN	N. C.	N. C.
Sundgren et al (39)	2015	72	MSSS BDI FSS BVRT Vocabulary Test COWAT Digit Span Test TMT Snellen charts	P300	A: N. C. V: ↑	A: ↑ V: N. C.
Triantafyllou et al (34)	1992	47	-	P300	↓	↑
Vázquez-Marrufo et al (35)	2009	26	-	P300	N. C.	↑
Vázquez-Marrufo et al (36)	2014	26	PASAT (3s) SDMT BDI-II	P300	↓	-
Vázquez-Marrufo et al (37)	2019	20	PASAT (3s) SDMT BDI	P300	N. C.	N. C.
Waliszewska-Prosól et al (45)	2018	30	PSS D-type Scale SDMT	P300	N. C.	↑
Whelan et al (25)	2010	33	PASAT (3s)	P300	A: N. C. V: ↓	A: ↑ V: N. C.
Zeng et al (46)	2017	24	**MMSE** **MoCA** HADS	P300	↓	↑

(Amp. = Amplitude; ERP = Event-Related Potential; Lat. = Latency; N = Number of MS patients included in each study; N. C. = No change).
Note: Although some studies obtained P300 through both auditory and visual modalities, only the different results were present separately.

Appendix 5 – Quality Assessment

Table 27 – Application of JBI Critical Appraisal Checklist to assess quality of each included study (adapted from (22)).

Authors	1	2	3	4	5	6	7	8
Amato et al (47)	Unclear	No	Yes	Yes	No	No	Yes	Yes
Artemiadis et al (40)	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes
Covey et al (48)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
El-din et al (41)	Unclear	Yes	Yes	Yes	No	No	Yes	Yes
Ellger et al (28)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Gedizlioglu et al (42)	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Gerschlager et al (29)	Unclear	No	Yes	Yes	No	No	Yes	Yes
Gonzalez-Rosa et al (26)	Unclear	No	Yes	Yes	Yes	Yes	Yes	Yes
Honig et al (27)	Unclear	No	Yes	Yes	No	No	Yes	Yes
Jung et al (30)	Unclear	Yes	Yes	Yes	No	No	Yes	Yes
Li (49)	Unclear	No	Yes	Yes	No	No	Yes	Yes
López-Góngora et al (43)	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Magnié et al (24)	Unclear	Yes	Yes	Yes	No	No	Yes	Yes
Matas et al (31)	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Piras et al (32)	Unclear	No	Yes	Yes	No	No	Yes	Yes
Pokryszko-Dragan et al (38)	Unclear	No	Yes	Yes	No	No	Yes	Yes
Pokryszko-Dragan et al (44)	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Santos et al (33)	Unclear	No	Yes	Yes	No	No	Yes	Yes
Sundgren et al (39)	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes

Triantafyllou et al (34)	Unclear	No	Yes	Yes	Yes	Yes	Yes	Yes
Vázquez-Marrufo et al (35)	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Vázquez-Marrufo et al (36)	Unclear	Yes	Yes	Yes	No	No	Yes	Yes
Vázquez-Marrufo et al (37)	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Waliszewska-Prosól et al (45)	Yes	No	Yes	Yes	No	No	Yes	Yes
Whelan et al (25)	Unclear	No	Yes	Yes	Yes	Yes	Yes	Yes
Zeng et al (46)	Unclear	Yes	Yes	Yes	No	No	Yes	Yes

(1 = Were the criteria for inclusion in the sample clearly defined?; 2 =Were the study subjects and the setting described in detail?; 3 = Was the exposure measured in a valid and reliable way?; 4 = Were objective, standard criteria used for measurement of the condition?; 5 = Were confounding factors identified?; 6 = Were strategies to deal with confounding factors stated?; 7 = Were the outcomes measured in a valid and reliable way?; 8 = Was appropriate statistical used?)